In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

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B. A., *	
*	No. 11-51V
Petitioner, *	
v. *	Special Master Gowen
*	
SECRETARY OF HEALTH *	Human Papillomavirus ("HPV");
AND HUMAN SERVICES, *	Alum Adjuvant; Headache Disorder;
*	Acute Disseminated Encephalo-
Respondent. *	myelitis ("ADEM").
* * * * * * * * * * * * * * * * * * * *	

Lisa A. Roquemore, Rancho Santa Margarita, CA, for petitioner.
Jennifer L. Reynaud, United States Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

On January 20, 2011, B.A. ("petitioner") filed a claim in the National Vaccine Injury Compensation Program ("Vaccine Act" or the "Program").[2] Petitioner received a second dose of the Gardasil vaccination for human papillomavirus ("HPV") (referred to hereafter as "the HPV vaccine") on January 23, 2008 and a third dose on June 3, 2008. Petitioner alleges that as a result of these vaccines, she suffered severe, chronic headaches and various other sequelae. Amended Petition at 1. The medical records and testimony reflect that B.A. did suffer these symptoms beginning approximately nine to ten days after the January 23 HPV vaccine; a decreased plateau; and an increase in symptoms within a similar timeframe after the June 3 HPV vaccine. Multiple specialists recorded that she experienced severe, chronic headaches. A more definitive diagnosis to explain her symptoms has not been reached.

[1] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), **because this opinion contains a reasoned explanation for the action in this case, I intend to post it on the website of the United States Court of Federal Claims.** The court's website is at http://www.uscfc.uscourts.gov. Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* **If neither party files a motion for redaction within 14 days of the date this decision is filed, the ruling will be posted on the court's website without any changes.**

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

Petitioner's expert in neurology and immunology, Dr. Lawrence Steinman, M.D. offered two theories. The first was that B.A.'s symptoms were best explained by a diagnosis of acute disseminated encephalomyelitis ("ADEM"), which was caused by molecular mimicry between components of the HPV strains in the vaccine and components of myelin basic protein at the blood-brain barrier. Dr. Steinman's second theory was that the HPV vaccine's antigens and alum adjuvant together can activate pro-inflammatory cytokines including IL-1β and stimulate the Nalp3 inflammasome and the trigeminal ganglion which provides sensory innervation to the dura and vasculature in the brain. He explained that activation of the primary sensory neurons in the brain is thought to be a crucial step in the pathogenesis of headaches.

Respondent opposed compensation. Respondent and his experts – Dr. Thomas Leist, M.D. (neurology and immunology) and Dr. Edward Cetaruk, M.D. (toxicology) acknowledged B.A.'s experience. Dr. Leist strenuously disagreed with the posited diagnosis of ADEM. He also critiqued the theories of causation and whether her symptoms increased after the June 3 vaccination. Dr. Cetaruk critiqued Dr. Steinman's invocation of the alum adjuvant. After a review of the entire record, for the reasons set forth below, I find that petitioner did not establish that she developed ADEM. However, I conclude that the second proposed theory was sound and reliable and fits the facts in this case. The timing was undisputed. Respondent has not established a more likely alternative cause for B.A.'s symptoms. Accordingly, she is entitled to compensation.[3]

I. Procedural History

Petitioner initiated her claim *pro se* on January 20, 2011. Petition (ECF No. 1). She subsequently retained counsel. On February 8, 2011, she filed an Amended Petition, in which she alleged that her second and third HPV vaccines caused, or in the alternative, significantly aggravated the development of chronic headaches and residual injuries. Amended Petition (ECF No. 33) at 1. Respondent elected to litigate the claim. Respondent's Rule 4(c) Report (ECF No. 34). In May 2013, petitioner moved her representation to the counsel of record. The case was moved to my docket in March 2014. The case was scheduled for an entitlement hearing.

In advance of the hearing, petitioner filed numerous reports from Dr. Lawrence Steinman, M.D., who opined on neurology and immunology. Petitioner's Exhibits ("Pet. Exs.") 59, 74, 89, 95. Respondent filed responsive reports on those subjects from Dr. Thomas Leist, M.D. Respondent's ("Resp.") Exs. A, I. Respondent also filed a report from Dr. Edward Cetaruk, M.D., who specializes in toxicology. Resp. Ex. G. The parties also filed their respective experts' curriculum vitae and significant medical literature. The parties filed respective pre-hearing briefs. Pet. Pre-Hearing Brief (ECF No. 100); Resp. Pre-Hearing Response (ECF No. 108); Pet. Pre-Hearing Reply (ECF No. 112). I directed the parties to file one joint prehearing submission. On February 18, 2016, the parties filed two versions with the explanation that they came to an impasse on certain language. Resp. Version of Joint Prehearing Submission (ECF No. 117); Pet. Version of Joint Prehearing Submission (ECF No. 118).

[3] Pursuant to Section 13(a)(1), in order to reach my decision, I have considered the entire record, including all of the medical records, expert testimony, and literature submitted by the parties. This decision discusses the elements of the record I found most relevant to the outcome.

On March 15-16, 2016, I held an entitlement hearing in Los Angeles, California. Petitioner's mother testified to the facts. Petitioner's expert Dr. Steinman and respondent's expert Dr. Leist also testified.[4] Transcript ("Tr.") (ECF Nos. 124, 126). On January 24, 2017, the hearing resumed for a third day in Washington, D.C. Respondent presented Dr. Cetaruk's testimony. Petitioner offered rebuttal from Dr. Steinman. Tr. (ECF No. 138). During the hearing, I asked Dr. Steinman about an article by Souayah et al., which petitioner had filed (along with considerable other medical literature) unaccompanied by an opinion from Dr. Steinman, after the parties had filed their pre-hearing briefs. *See* Pet. Ex. 104; discussed at Tr. 562-63, 573-78. Following the hearing, petitioner filed an additional report from Dr. Steinman. Pet. Ex. 128. Respondent filed a responsive report from Dr. Leist. Resp. Ex. L. The parties filed post-hearing briefs. Pet. Post-Hearing Brief (ECF No. 147); Resp. Post-Hearing Response (ECF No. 148); Pet. Post-Hearing Reply (ECF No. 148). This matter is now ripe for adjudication.

II. General Legal Standards for Adjudication[5]

The Vaccine Act was established to compensate vaccine-related injuries and deaths. §300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, *reprinted in* 1986 U.S.C.C.A.N. at 6287, 6344).

A petitioner bears the burden of establishing his or her entitlement to compensation from the Vaccine Program. A petitioner's burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). A petitioner may demonstrate entitlement in one of two ways. The first way is to show that she suffered an injury listed on the Vaccine Injury Table, beginning within the requisite time period set forth on the Table (a "Table injury"), in which case, causation is presumed. 42 C.F.R. § 100.3. In the present case, B.A. does not allege a Table injury. Thus, she bears the burden of establishing actual causation. § 300aa-13(a)(1); *Cedillo v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010). To establish actual causation, petitioner must provide: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between the vaccination and injury." *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

[4] Respondent's counsel generally submitted Dr. Leist's reports in lieu of direct testimony. However, Dr. Leist did offer limited testimony on direct and on cross-examination. Tr. 308-09.

[5] Decisions of special masters and the U.S. Court of Federal Claims (some of which are referenced in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

The preponderance of the evidence standard requires a petitioner to demonstrate that it is "more likely than not" that the vaccine caused her injury. *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 n. 2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, petitioner must demonstrate that the vaccine was "not only [a] but for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006).

The special master must consider the record "as a whole" and may not rule in a petitioner's favor solely based on his or her own claims, "unsubstantiated by medical records or medical opinion." § 13(a)(1). In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (providing that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus, a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether petitioners have met their burden of proof. "Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury. . . . Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009) (referencing *Althen*, 418 F.3d 1274; *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317 (Fed. Cir. 2006)).

Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention so long as the petitioner supplies the medical opinion of an expert. *Id.* at 1279–80. The court also indicated that, in finding causation, the fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id.* at 1280.

III. Experts

1. Legal Standard

In Vaccine Act cases, expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339. "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 n.2

(Fed. Cir. 1999) (citing *Daubert*, 509 U.S. at 592-95). In Vaccine Program cases, these factors are used in the weighing of the scientific evidence actually proffered and heard. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66–67 (Fed. Cl. 2010) ("uniquely in this Circuit, the Daubert factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011); *see also Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 742–45 (2009).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

2. Petitioner's Expert Dr. Lawrence Steinman

Petitioner submitted five reports and testimony from Dr. Steinman, a board-certified neurologist. Pet. Ex. 50 at 2. He received a bachelor's degree from Dartmouth College and a medical degree from Harvard University, where he was also an NIH fellow. *Id.* at 1. After medical school, he completed an internship in surgery and residencies in pediatrics and pediatric and adult neurology at Stanford University. *Id.* He joined the faculty of Stanford University in 1980. *Id.* He is currently a professor of neurological sciences, neurology, genetics, and pediatrics. He is also the chair of the university's interdepartmental program in immunology. *Id.*; Pet. Ex. 49 at 2. He has received awards for his contributions to research on multiple sclerosis ("MS"); neuroscience; and immunology. Pet. Ex. 50 at 2. At the entitlement hearing in January 2016, Dr. Steinman estimated that his work at Stanford is 70% research; 25% clinical; and 5% administrative/ teaching. Tr. 86. He has personally researched molecular mimicry between the human papillomavirus and myelin basic protein. Tr. 84. In his clinical practice, he has treated ADEM, headaches, movement disorders, dystonia, memory loss, and fatigue. Tr. 86-91. However, he has received the most recognition for his expertise and research on MS. Pet. Ex. 50 at 2; Pet. Ex. 59 at 2. Dr. Steinman has authored numerous publications and was elected to the National Academy of Medicine (formerly known as the Institute of Medicine). Tr. 92. Dr. Steinman is also an invited member of the National Academy of Sciences. I accepted Dr. Steinman as an expert in neurology and immunology. Tr. 94.

3. Respondent's Expert Dr. Thomas Leist

Respondent presented two reports and testimony from Dr. Leist, who is board-certified in neurology and psychiatry. Resp. Ex. B at 1; Tr. at 111. After obtaining a doctorate in biochemistry at the University of Zurich in Switzerland, he received a medical degree from the University of Miami. *Id.* at 1. Since 2000, he has served on the faculty of Thomas Jefferson University, where he is currently a Professor of Neurology, head of the MS fellowship program, and chief of the clinical neuroimmunology division at the university's comprehensive MS center. *Id.* Dr. Leist primarily treats patients with MS, but also sees patients who are suspected to have MS but have a broader differential diagnosis (such as ADEM). Tr. 296. He also conducts *ex vivo*, imaging, and cognitive research on that patient population. *Id.* He has not conducted research on ADEM. Tr. 314. Like Dr. Steinman, Dr. Leist has published many times and is a member of several respected societies. I accepted Dr. Leist as an expert in neurology and immunology. Tr. 298.

4. Respondent's Expert Dr. Edward Cetaruk

Respondent also presented one report and testimony from Dr. Cetaruk, who is board-certified in medical toxicology and emergency medicine. Resp. Ex. H at 1. He received a bachelor's degree from the University of Massachusetts at Amherst and a medical degree from New York University. *Id.* He then completed fellowships in medical toxicology and emergency medicine research, followed by a residency in emergency medicine. *Id.* Dr. Cetaruk now teaches medical toxicology at the University of Colorado. He sees patients at several hospitals and in occupational settings, both in emergency and routine situations. Tr. 401-02. Some individuals present with a known exposure or overdose, but for others he runs a full diagnostic workup. Tr. 403-04. I accepted Dr. Cetaruk as an expert in toxicology. Tr. 407.

IV. Summary of Relevant Facts

1. Predating the Vaccinations at Issue

B.A. was born in the fall of 1991. She grew up in Alabama. In 2000, when B.A. was nine years old, her parents amicably divorced. Her father remarried. B.A. continued to live with her mother, who started dating a new boyfriend in 2000. Her mother's boyfriend had a daughter who was about the same age as B.A. The girls got along well. B.A. never went to therapy or counseling. Tr. 7-10.

In May 2003, a gastroenterologist diagnosed functional recurrent abdominal pain, for which he recommended antihistamines and a high-fiber, GER diet. Pet. Ex. 1 at 72-74. That month, B.A. also underwent a brain CT scan. The reason for the procedure was "headaches." The impression was negative. Pet. Ex. 1 at 67. From 2003 – 2007, B.A.'s primary care provider Dr. Gao recorded intermittent headaches associated with abdominal pain, viral infections, and/ or strep throat. Pet. Ex. 1; Pet. Ex. 30 at 2 (January 2007 urgent care visit for stomachache, dizziness, chills, and headache). From 2005 – 2007, B.A. periodically went to a chiropractor, Dr. McCurdy for low back pain and knee pain associated with cheerleading competitions. Pet. Ex. 16. During this period, annual ophthalmology records mention "some" headaches. Pet. Ex.

4. An August 2007 comprehensive ophthalmology exam detailed that B.A. had "headaches every now and then when she stays on the computer too long." Pet. Ex. 4 at 9.

In spring 2007, B.A. completed ninth grade. She was earning As and Bs. She rarely missed school and she participated in many extracurricular activities. She was selected to participate in the People to People student ambassador program. Pet. Ex. 72 at 2; Tr. 11-14. As part of that program, she went to seven European countries over three weeks in summer 2007. When she returned, she was exhausted. On July 11, 2007, Dr. Gao recorded a two-week history of sore throat, cough, and pharyngitis. Pet. Ex. 20 at 19. Her mother said that this resolved. Tr. 14-15.

In fall 2007, B.A. began tenth grade. Tr. 9. Twice in September 2007, she reported gastrointestinal issues to Dr. Gao. Pet. Ex. 1 at 20,[6] 18. Due to these issues, she was hospitalized for one day at Jacksonville Medical Center. Pet. Ex. 2 at 72-78. An x-ray of the upper gastrointestinal tract revealed no abnormalities. Pet. Ex. 1 at 43. On October 11, Dr. Gao recorded that B.A. was experiencing dizziness, losing her voice, and throat soreness. Pet. Ex. 1 at 17. Her mother testified that B.A. had a stomach virus, but she recovered before an October trip to Disneyworld. Tr. 15.

Her mother testified that before B.A. received any HPV vaccinations, B.A. sometimes experienced headaches. These were associated with sinus irritation, nasal congestion, and seasonal allergies. They were "dull." They usually resolved upon taking Tylenol, ibuprofen, and/or allergy medicine. Pet. Ex. 72 at 1; Tr. 13-14.

On November 12, 2007, B.A. received the first dose of the HPV vaccine at Dr. Gao's office. Dr. Gao did not record any complaints. Pet. Ex. 1 at 4, 16. Dr. Gao's next record is from November 27, 2007. He wrote that B.A. had "chills, low grade fever, muscles tight in neck, been sick since returning from Europe in July." He also circled "nausea" and "vomiting." A mono test was negative. Pet. Ex. 1 at 15.

2. Second HPV Vaccination and Subsequent History

On January 23, 2008, B.A. returned to Dr. Gao, who recorded that B.A. was on over-the-counter cold medications and "pro hist." He circled "cough." Pet. Ex. 1 at 14. Her mother recalled asking whether B.A. should be vaccinated in light of the cough, but Dr. Gao said it was fine. Tr. 16-17. Her pain level was 0 / 10. Dr. Gao administered the second HPV vaccination. Pet. Ex. 1 at 4, 14.

At the end of January, B.A. developed headaches and fatigue. Tr. 18; Pet. Ex. 35 at 1; Pet. Ex. 72 at 2. She stayed home from school. Tr. 24. On January 30, Dr. Gao recorded that B.A. had cough, congestion, headache, sore throat, and fatigue. Her pain level was 6 / 10. A strep test was negative. Pet. Ex. 1 at 13. On February 5, Dr. Gao recorded a productive cough, a

[6] Respondent's expert Dr. Leist says that on September 7, B.A. also "presented with headache." Resp. Ex. A at 2. The record from this visit is handwritten. I do not see a clear notation of headache. There is a faint notation that could represent "HA" but it is not clear.

3 - 4 day history of headache, sore throat and neck, fever, nausea, and light sensitivity. Her pain level was 6 / 10. *Id.* at 12. A chest x-ray that same day was unremarkable. *Id.* at 42.

On February 8, 2008, an otolaryngologist Dr. Brown recorded B.A.'s complaints of headaches. On physical examination, he found minimal tenderness over the frontal sinus area to percussion. His assessment was chronic migraine-type headaches and chronic sinusitis. He prescribed Midrin for the headaches, Norco for other body aches, and also Avelox and Ed Bron-G. Pet. Ex. 34 at 1. A CT scan found that her nasal septum was mildly deviated to the left but was otherwise unremarkable. Pet. Ex. 34 at 2.

On February 13, 2008, Dr. Gao recorded that her pain was at 10 / 10. Pet. Ex. 1 at 11. He referred her to Dr. Gehi at Anniston Neurology & Headache Management Center. Dr. Gehi recorded that B.A.'s past history included mild headaches, which she had been able to sleep off. Dr. Gehi recorded that B.A. had sinus problems 2 ½ weeks prior (which would date back to approximately January 27). The sinus problems got better. However, 11 days prior (which would date back to February 3), B.A. began having a constant, throbbing frontal headache. It seemed to be aggravated by movement. It was associated with nausea. She was also experiencing blurry vision, photophobia, phonophobia, and insomnia. She denied any syncope. Dr. Gehi suspected a chronic migraine/ muscle contraction headache, but because it was not getting better, she found it necessary to rule out organic etiology. She prescribed Corgard, Elavil, and Anaprox. Pet. Ex. 24 at 8-9. She ordered a head MRI and an EEG, which were normal. Pet. Ex. 3 at 10-12.

B.A. then had three appointments with a chiropractor, Dr. Wheeler for her headache pain. Pet. Ex. 18 at 6-11. Additionally, on February 26, 2008, B.A. went to the emergency room at Children's Hospital of Alabama, where she was given Corgard, Compazine, Toradol, and Solumedrol. Pet. Ex. 31 at 32-38.

On February 28, 2008, Dr. Gehi recorded that B.A. was not getting better. Her assessment was chronic migraine headaches, snoring, and depression. She recommended IV DHE treatment and possibly a spinal tap and other testing. She increased the prescription for Corgard; provided Toradol and Phenergan; and also prescribed DHE and Reglan. Pet. Ex. 24 at 6. On March 3, an ophthalmologic evaluation was unremarkable. Pet. Ex. 4 at 6-8.

On March 6, 2008, a gynecologist, Dr. Young, saw B.A. for evaluation of chronic headaches. Either Dr. Gao (who made the referral) or another physician had wanted B.A. "evaluated for possible pituitary adenoma with hormone levels." Dr. Young did not record her assessment, only that she "reviewed the potential causes for this with" B.A. She gave B.A. magnesium oxide and Klonopin. Pet. Ex. 32 at 9. Dr. Young ordered labwork, which showed elevated testosterone (86 ng/dL; reference range 14 - 76 ng/dL). Pet. Ex. 2 at 71.

On March 10, 2008, B.A. went to the emergency room at Children's Hospital complaining of headaches. The history of present illness provides that she had no significant prior medical history and presented with headache of gradual onset of 4-5 weeks. A lumbar puncture was completed on the second attempt. The opening pressure was 16 cm of water,

which is normal.[7] The lumbar puncture obtained "approximately 3-4 ml of clear spinal fluid." The procedure note provides that the CSF was "unremarkable." However, the lab results record that the CSF protein was 49 mg/dL ("high" compared to normal range of 15 – 45 mg/dL). CSF glucose was in normal range. 0 white blood cells were recorded, but a gram stain indicated: "rare – WBC's seen." 770 red blood cells were recorded "high" (a normal finding would be 0). Pet. Ex. 31 at 13-16.[8]

On March 17, 2008, an allergist, Dr. Grubbe, ordered labwork which did not find detectable levels of any allergens. Pet. Ex. 27 at 2-3, 7.[9] On March 19, Dr. Young recorded a telephone call from B.A.'s mother, who stated that B.A.'s headaches seemed worse around the time of her menstrual cycle. They agreed to try an oral contraceptive, Femcon, in hopes that it would alleviate the headaches. Pet. Ex. 32 at 8.

On March 20, 2008, another neurologist, Dr. Valero-Fonseca at Children's Hospital, had an initial evaluation with B.A. Her primary complaint was a 7-week history of continuous, bi-frontal headaches. Pet. Ex. 31 at 1-3. On a checklist, the following symptoms were selected: fatigue, weight gain, decreased activity, eye pain, pain from bright lights, earaches, ringing in ears, nausea, vomiting, abdominal pain, back pain, joint pain, weakness, dizziness, depression, anxiety, memory loss, and cold intolerance. *Id.* at 7-8. Dr. Valero-Fonseca assessed that B.A. was experiencing tension headaches, but "her main problem [was] anxiety and depressed mood, [which were making] her headaches worse in despite of multiple analgesic medication." Dr. Valero-Fonseca recommended therapy or counseling to address the depression and anxiety. Pet. Ex. 31 at 5.

On March 21 and 24, 2008, B.A. saw a chiropractor, Dr. Bolton. Pet. Ex. 19. On March 25, a pain management specialist, Dr. Maddox, saw B.A. for the first time. He recommended a mild muscle relaxant. He considered degenerative disc disease of the cervical spine and left C5 radicular pain. Pet. Ex. 7 at 1-2. However, a cervical spine MRI was normal. Pet. Ex. 7 at 3.

On April 1, 2008, an orthodontist, Dr. Taylor, recorded that B.A. had continuous headaches on both sides and various other issues including muscle pain in her jaw, head, neck, and back, and teeth clenching. A radiograph showed a class I occlusion with a limited range of opening. Dr. Taylor's assessment was acute TMJ synovitis with masticatory myalgia. He prescribed a limited course of Mobic to control inflammation. He instructed B.A. to wear a bite plate at night, stop consuming caffeine, and stop chewing gum. Pet. Ex. 15 at 5-6.

On April 14, 2008, Dr. Gao recorded that she was still having headaches and her pain was at 6 / 10. Pet. Ex. 1 at 10. That month, she also followed up with the chiropractor Dr. Wheeler. Pet. Ex. 18 at 3-4. On April 22, B.A. followed up with the gynecologist Dr. Young,

[7] In contrast, a pressure of 20 cm of water or above is considered abnormal and indicative of increased spinal pressure. Mosby's Medical Dictionary (5th ed. 2014) at 651.

[8] Various medical records provide that after this lumbar puncture, B.A.'s headaches improved for some period of time.

[9] Her mother believed that B.A. had seasonal allergies, specifically to pollen. However, B.A. was "low/ fail" for a pollen allergy when tested by Dr. Grubbe. Tr. 29.

who recorded that starting the oral contraceptive did not seem to have any effect on B.A.'s headaches. Since the headaches began, B.A. had been out of school. B.A. and her grandmother requested a letter excusing B.A. from school for the rest of the year because of the headaches. Dr. Young declined because she did not believe B.A.'s problem was gynecological. She felt it was more appropriate for a pediatrician or neurologist to write such a letter. Pet. Ex. 32 at 6.

B.A. returned to school in April 2008. While her grades had slipped, she completed the tenth grade and was allowed to progress. She was unhappy and frustrated about her medical issues. However, the symptoms leveled out. The severity of her symptoms was about a 6 out of 10. Pet. Ex. 72 at 2-3; Tr. 35-38.

3. Third HPV Vaccination and Subsequent History

On June 3, 2008, Dr. Gao administered the third HPV vaccination (as well as the first Hepatitis B and second varicella vaccinations). He recorded that B.A. was still having headaches, her pain was at 2 / 10, and that she should follow up with a neurologist. Pet. Ex. 1 at 3-4, 9; Tr. 36.

On June 4, 2008, B.A. saw a pediatric gastroenterologist, Dr. Cavender. His impression was "chronic migrainous headaches and nausea/ vomiting . . . possibility of abdominal migraines and cyclic vomiting." He prescribed Protonix and Periactin. Pet. Ex. 33 at 3-5.

On June 6, 2008, B.A. began seeing a psychiatrist, Dr. Archibald, because her treating physicians wanted to rule out stress, tension-related headaches, and depression. B.A. had not received any past psychiatric or psychological treatment. She denied any problems with school, peers, or family; any stressors in the past year (other than the headaches); or any history of abuse. A mental status examination was normal. Dr. Archibald recorded B.A.'s assessment of the headaches to a severity of 6 / 10. B.A. and her mother, who was present for at least part of the evaluation, reported many of the symptoms already noted above. They specifically reported that B.A. had a heightened sense to light and sound. She had asked her mother, who was sitting in another room, to stop turning the pages of a book because the sound was so loud. Pet. Ex. 29 at 6-8.

On June 10 – 11, 2008, Dr. Gehi had B.A. undergo a night polysomnography study, which did not find obstructive sleep apnea. The impression was primarily snoring followed by chronic persistent headache, probable poor sleep hygiene, and obesity. Dr. Gehi recommended improved sleep hygiene, weight reduction, and resuming certain medications. Pet. Ex. 3 at 1-6.

B.A.'s mother testified that around this time, within 1-2 weeks after the third HPV vaccination, B.A.'s headaches and other symptoms escalated to about 8 - 9 / 10. B.A. also developed muscle spasms and was very cold, even though it was summer. Tr. 38.

On June 24, 2008, B.A.'s mother called Dr. Young again. She reported that since beginning Femcon that spring, B.A.'s headaches and moods had improved. Afterwards, B.A. received the third HPV vaccination and her headaches got worse. B.A.'s mother asked whether there was a relationship between the HPV vaccinations and B.A.'s symptoms. Dr. Young indicated that according to the Physician's Desk Reference, the HPV vaccination was associated with the same symptoms as a placebo. Pet. Ex. 32 at 4; Tr. 42.

On July 10, 2008, the psychiatrist Dr. Archibald recorded under "new problems": "The H/A spiked after" a HPV vaccine. She showed "mild" progress. Dr. Archibald decided to increase her Zoloft prescription. Pet. Ex. 29 at 4.

B.A.'s mother recalled that she also called Dr. Gao's office about B.A.'s symptoms and whether they were possibly related to the HPV vaccinations. Tr. 44. On July 28, 2008, Dr. Gao's practice submitted a VAERS report that B.A. had received two doses of the HPV vaccine and had suffered headaches. The reported onset date was February 13, 2008. Pet. Ex. 1 at 1-2.

On July 31, 2008, on referral from Dr. Archibald, a neuropsychologist Dr. Carter conducted an evaluation. Pet. Ex. 5. It does not appear that Dr. Carter reviewed any medical records. She took a history from B.A. and her mother. They reported that B.A. did not have any prior issues, but that after the second HPV vaccination, B.A. developed severe headaches with secondary issues including nausea, fatigue, dizziness, blurred vision, and changes in taste and smell. She had heightened sensitivity to noise, which exacerbated her headache pain. She also had difficulty with concentration and short-term memory, insomnia, teeth grinding, depression, and anxiety. Dr. Carter noted that B.A. had not received a diagnosis and that various treatments had been unsuccessful. B.A. assessed her current headache pain symptoms at 8 / 10. B.A. also reported that "the previous evening, after taking Imitrex, her headache pain was severe and she rated the severity as an 11/10." Pet. Ex. 5 at 6. After administering numerous psychological and cognitive tests, Dr. Carter found no evidence of neurocognitive impairment. B.A. endorsed various statements that were associated with depression, anxiety, and somatic concerns. Dr. Carter's impression was severe generalized anxiety disorder; depressive disorder; undifferentiated somatoform disorder; and dependent, avoidant, depressive, and obsessive-compulsive features. She wrote: "The severity of B.A.'s self-reported psychiatric symptomatology appears to be an extreme reaction to the onset of headache disorder and other somatic symptomatology. There is a significant likelihood that preexisting psychiatric disturbance (predating the onset of B.A.'s headache disorder) may explain B.A.'s extreme and unusual response to the [HPV] vaccine." Pet Ex. 5 at 15. Dr. Carter recommended continuing psychiatric treatment with Dr. Archibald and suggested additional psychopharmacological treatment as well as psychotherapy.

On August 4, 2008, the gastroenterologist Dr. Cavender recorded B.A.'s continued complaints of vomiting and nausea. Pet. Ex. 33 at 1-3. On August 5, B.A. saw the chiropractor Dr. Wheeler. Ex. 18 at 2.

On August 7, 2008, B.A. and her mother went to celebrate the mother's boyfriend's birthday. While B.A. was driving home, her headache worsened. She also experienced spasms and "stabbing pains" in her back. She had to pull over. They went to chiropractor Dr. McCurdy late that evening. It took almost two weeks for B.A. to move easily again. Tr. 48-49; Pet. Ex. 72 at 3; Pet. Ex. 16 at 18.

On August 8, 2008, B.A. returned to Dr. Gao, who recorded pain with movement, back muscle spasms, and shooting pains. Her pain was at 10 / 10. She also had an ophthalmology consult which was normal. Pet. Ex. 4 at 1-2. She began seeing another chiropractor, Dr. Callahan for her headaches and other symptoms. Pet. Ex. 37 at 1-2.

In August 2008, B.A. began 11th grade. Pet. Ex. 72 at 3. On September 2, 2008, another neurologist, Dr. Strong, conducted an initial consult. He recorded that B.A.'s mother had concluded that the headaches were related to the HPV vaccinations. Dr. Strong had not heard of that before and decided to begin with treating this like a "chronic daily headache." He prescribed Amerge and prednisone. He increased Topamax, because "she said her headache felt better after the spinal tap." He instructed B.A. to exercise consistently, stop drinking decaffeinated tea, and stop taking hormonal birth control. Pet. Ex. 9 at 14. In September, B.A. saw the chiropractor Dr. Wheeler. Pet. Ex. 18 at 1. She also returned to the psychiatrist Dr. Archibald. Pet. Ex. 29 at 2-3. On October 3, B.A. went to Jacksonville Medical Center complaining of headaches, migraines, nausea, vomiting, and muscle spasms. Pet. Ex. 2 at 49-54.

On October 14, 2008, the neurologist Dr. Strong recorded that the Amerge and prednisone he prescribed were not effective. B.A. was on B2, Slow-Mag, and Topamax. Dr. Strong administered a first course of Indocin and within one week, the headaches decreased in severity from 9 /10 to 5 - 6 / 10. He also prescribed Valium for the muscle spasms. Dr. Strong noted that he did not find any medical literature associating the HPV vaccination with headaches but he did find internet posts on the subject. Pet. Ex. 9 at 11-12.

Dr. Strong admitted B.A. to Trinity Medical Center from November 6 - 8, 2008. Dr. Strong wrote regarding the March 10, 2008 lumbar puncture: "Family thought [opening pressure] was 15. Spinal fluid was reportedly normal." Pet. Ex. 9 at 9. Dr. Strong obtained the lumbar puncture results. He wrote: "Opening pressure was 16. White count was 0, red count 770, protein 0.9, glucose 62." *Id.* This notation regarding the protein level is strange, as that result was actually 49 mg/dL (high compared to the reference range). *See* Pet. Ex. 31 at 13-16. Dr. Strong administered a course of intravenous dihydroergotamine ("IV DHE"), Toradol, and Depacon. This did not help. A second course of Indocin did not help. Indeed, her condition worsened. Pet. Ex. 9 at 9-12; Pet. Ex. 10 at 19-22.

B.A.'s mother recalls that due to the unsuccessful Indocin treatment, one of B.A.'s doctors pulled her out of school for six weeks. During this time, her school should have provided a tutor, but did not do so until January 2009. B.A. fell behind. Pet. Ex. 72 at 4.

On November 18, 2008, B.A.'s mother submitted a VAERS report addressing all of B.A.'s three HPV vaccinations. Pet. Ex. 23. She testified that she was not aware that Dr. Gao's office had previously submitted a VAERS report and she wanted to make sure there was one submitted to document B.A.'s issues. Tr. 54. On November 19, Dr. Strong's neurology colleague, Dr. Russell, saw B.A. and prescribed Lyrica. Pet. Ex. 9 at 8.[10] B.A.'s mother testified that at Christmas 2008, B.A. found it painful to move her fingers and hands. After that, her muscles and joints began to hurt. She had difficulty controlling and moving the left side of her body. Tr. 56-58.

On January 5, 2009, B.A. went to Jacksonville Medical Center for headaches and weakness. Pet. Ex. 2 at 35-40. Her mother testified that B.A. was able to "drag" her body to the car with assistance. Tr. 57. A CT scan of her head was unremarkable. Pet. Ex. 2 at 48. On

[10] Also in December 2008, B.A.'s menstrual period decreased or stopped entirely. It did not return until July 2009. *See* Pet. Ex. 13 at 11; Pet. Ex. 21 at 3.

January 6, Dr. Strong's assessment was chronic daily headaches, muscle spasms, and "probable" fibromyalgia. Dr. Strong prescribed Dilaudid and Flexeril, and increased Lyrica. MRIs of the brain and cervical spine were unremarkable. Pet. Ex. 9 at 3-5, Pet. Ex. 10 at 14-15.

On January 20, 2009, Dr. Strong prescribed Neurontin because B.A.'s insurance would not cover Lyrica. He noted that the Mayo Clinic had "turned [B.A.] down,"[11] but B.A. had secured an appointment at the Diamond Headache Clinic. Pet. Ex. 9 at 3-4. On January 26, a heavy metals test was normal except for elevated arsenic. Pet. Ex. 2 at 33-34. But on February 28, a repeat heavy metals test was normal. Pet. Ex. 2 at 31-32.

On February 24, 2009, B.A. transferred to a different primary care physician, Dr. Ulrich, D.O., C.M.D. He recorded an upper respiratory infection, as well as B.A. and her mother's account that her headaches were caused by the HPV vaccinations. He prescribed Keflex, Eda Histo, Zoloft, and Zanaflex. Pet. Ex. 22 at 13-14; Tr. 64-65.[12]

Following a referral from Dr. Strong, rheumatologist Dr. Bell saw B.A. on March 18, 2009. Dr. Bell planned to research the association between injections, headache, and soft tissue rheumatism. He recommended treatment for soft tissue rheumatism, physical therapy, and adequate sleep. He planned a trial of Sinemet. Testing of CBC, CRP, sedimentation rate, ANA, chemistry panel, CPK, urinalysis, hemoglobin A1c, and TSH were all normal. Pet. Ex. 17 at 1-6.

On April 15, 2009, B.A. had an initial consult with Dr. Merle Diamond at the Diamond Headache Clinic in Chicago, Illinois. Dr. Diamond recorded that B.A. had a neurologic disorder (headaches and muscle spasms), anxiety, and depression since 2008. B.A. had not been in school since mid-November 2008. She was being home-tutored but was nine weeks behind. Pet. Ex. 13 at 10.

Dr. Diamond admitted B.A. to St. Joseph's Hospital for testing and treatment. Dr. Diamond recorded that the earlier March 10, 2008 lumbar puncture had been associated with an improvement in B.A.'s headaches. Dr. Diamond ordered a repeat lumbar puncture, which was performed on April 17. It showed a CSF protein of 22 mg/dL. Her SED rate was high at 17. Pet. Ex. 13 at 8-13, 28; Pet. Ex. 28 at 75.[13] MRI, MRA, and MRV tests of the brain were unremarkable. Pet. Ex. 13 at 20-25. B.A.'s mother recalled that Dr. Diamond administered a set of injections, which lowered B.A.'s headaches from 8 / 10 to 5 / 10. On April 22, because B.A.'s insurance ran out, she was discharged with plans to follow up with Dr. Diamond in June. Pet. Ex. 13 at 27-28. B.A.'s mother testified that when they were in the airport preparing to head home, B.A.'s headaches increased again to a 9 - 10 / 10. Tr. 61.

[11] B.A.'s mother testified that the Mayo Clinic did not accept B.A. as a patient because she was under 18. Tr. 58.

[12] Dr. Ulrich's record provides that he had not seen B.A. "since 2002." Pet. Ex. 22 at 13-14. Petitioner did not file any earlier records from Dr. Ulrich.

[13] *Compare to* Pet. Ex. 31 at 15-16 (March 10, 2008 lumbar puncture finding elevated CSF protein of 49 mg/dL).

On May 22, 2009, testosterone was elevated (119 ng/dL; reference range 14 - 76 ng/dL). Pet. Ex. 2 at 30. Between June 2 – 29, B.A. attended eight physical therapy appointments with a Dr. Wilhoite. At the end of that period, she reported some relief. The headaches were less intense and shorter in duration. Pet. Ex. 11.

On June 15, 2009, Dr. Diamond recorded that B.A.'s headaches had continued. B.A. wanted to receive Dr. Diamond's protocol again, but at her local hospital so that her insurance would cover it. Pet. Ex. 13 at 2-7. However, her primary care provider Dr. Ulrich declined to administer the Diamond protocol because it was out of his expertise and the hospital would not allow him to be directed by another physician in a different state. Pet. Ex. 22 at 11.

During the June 15, 2009, follow-up, Dr. Diamond also instructed B.A. to see a gynecologist or endocrinologist regarding her elevated testosterone. Pet. Ex. 13 at 2-7; Pet. Ex. 32 at 2-3; Pet. Ex. 21 at 3-5. On July 27, Dr. Stradtman, a specialist in adolescent gynecology and reproductive endocrinology, conducted an initial evaluation. Dr. Stradtman summarized that since the March 2008 finding of elevated testosterone, B.A. had been taking oral contraceptives. She had regular menses until December 2008, then no menses until July 2009. Repeat bloodwork found elevated testosterone (87 ng/dL; reference range 14 - 76 ng/dL) as well as elevated insulin. Pet. Ex. 21 at 3-5, 12, 14.

B.A.'s mother testified that from summer 2009 – summer 2010, B.A. was somewhat stabilized on medication. Her headaches were steadily at a 6 or 7 out of 10. They occasionally went to the emergency room. Tr. 69-70. B.A. scored well on the ACT standardized test and was accepted with a scholarship to college. Pet. Ex. 72 at 5. On June 16, 2010, the primary care provider Dr. Ulrich recorded that B.A.'s headaches had dropped down to about a 5-6. Since B.A. had learned to adjust to the headaches, she went off "most of her medicines." But then the headaches shot back up to a 9-10 every day. "In addition to this headache, [she had] developed twitching. It is almost like a tic, repetitive behaviors, moving her arms, swinging her arm, jerking her head." Dr. Ulrich's assessment was headaches and movement disorder. He prescribed Keppra, Trazodone, and Zoloft. Pet. Ex. 22 at 10.

In summer 2010, a coworker told B.A.'s mother about Dr. Wu, a chiropractor in Destin, Florida (which is approximately a 5-hour drive from their home in Alabama). B.A. began seeing him, approximately twice each month. Pet. Ex. 12 at 5-7. B.A.'s mother stated that Dr. Wu's treatment significantly improved B.A.'s condition. However, B.A. started college in August 2010. She needed to maintain a full course load to maintain her scholarship. She had less time to go to Dr. Wu. Her condition worsened and she missed class. Pet. Ex. 72 at 5; Tr. 71.

On September 20, 2011, Dr. Ulrich observed that "every 15 seconds or so, she will have a rotation of her head with jaw movements." He recorded this was uncontrolled. He prescribed Zanaflex and endorsed continuing the acupuncture with Dr. Wu. Pet. Ex. 22 at 9. On September 27, B.A. went to Jacksonville Medical Center complaining chiefly of neck pain. It was also recorded that her headaches, muscle spasms, tics, and stuttering speech had worsened over the past three weeks. Pet. Ex. 2 at 16.

On October 15, 2010, Dr. Ulrich recorded that over the past month, B.A. had regressed some and her headaches were more severe. He increased Keppra. Pet. Ex. 22 at 8. He wrote a letter recommending B.A.'s medical withdrawal from college due to the worsening of the headaches. He also gave B.A.'s mother a FMLA leave. Pet. Ex. 22 at 18.

On December 9, 2010, the gynecologist Dr. Young recorded B.A.'s concerns about potential infertility issues. He did not think this was a concern because B.A. was having normal cycles but he offered a referral to a reproductive endocrinologist. He also recommended going to a rheumatologist regarding the muscle spasms. Pet. Ex. 32 at 2. Bloodwork again showed elevated testosterone (111 ng/dL, reference range 6-82 ng/dL). This record from Dr. Young has a handwritten note: "↑ testosterone [mildly elevated]. Add to problem list. Female hormones appear ALL NL [presumably normal]. I would have patient see reproductive endocrinologist." Pet. Ex. 6 at 17.

B.A. saw Dr. Ulrich for upper respiratory infection/ flu symptoms on December 14, December 21, and March 7. Pet. Ex. 22 at 5-7. On March 15, 2011, Dr. Callahan, the chiropractor whom B.A. began seeing in August 2008, wrote a letter "to whom it may concern," summarizing B.A.'s history and opining that B.A. "either had a reaction to something within the [HPV vaccines], or her immune system became overwhelmed by the introduction of the vaccines and could never fully recover." Pet. Ex. 26.[14]

On March 29, 2011, the gynecologist/ endocrinologist Dr. Stradtman saw B.A. regarding the elevated testosterone and other issues. His assessment was oligomennorrhea with androgen excess and mild abnormal hair growth; mild PCOS; acanthosis nigricans; overweight with weight gain; insulin resistance; mild dysmenorrhea; and chronic headaches. B.A. did not want to take oral contraceptives. Dr. Stradtman recommended spironolactone as well as prometrium if her period did not resume. Pet. Ex. 21 at 1-2.

B.A.'s mother recalled that upon B.A.'s medical withdrawal in fall 2010, her college agreed to extend her scholarship for one year. Tr. 72. B.A. returned for the fall 2011 semester. Pet. Ex. 72 at 5. However, in September 2011, she went to the emergency room several times complaining of involuntary twitching/ dystonic movements of her head. This also made her uncomfortable, self-conscious in public, and unable to drive. Pet. Ex. 72 at 5; Tr. 75-76.

In October 2011, the neurologist Dr. Strong recorded that B.A. had chronic daily headaches, fibromyalgia, muscle spasms, dystonia, left hemiparesis, and severe memory loss. He ordered bloodwork and an MRI of the brain, which were both unremarkable. Pet. Ex. 43 at 1-5. Also in October 2011, Dr. Ulrich wrote a letter "to whom it may concern," that B.A.'s headaches had continued. Additionally, the involuntary head movements were incapacitating and could only be treated by heavy sedation. Due to these issues, Dr. Ulrich supported her medical withdrawal from college. Pet. Ex. 40 at 11. An administrator said that if B.A. improved

[14] I note that before Dr. Callahan wrote this letter, B.A. and her family were already concerned that the vaccines caused her symptoms. Tr. 42; Pet. Ex. 32 at 4; Tr. 11; Pet. Ex. 22 at 13-14. Additionally, B.A. had already filed this claim.

and wanted to return, she could ask for the scholarship to be reinstated – but that was not guaranteed. Pet. Ex. 72 at 5; Tr. 75-76.

During 2012 - 2014, B.A. continued with Dr. Ulrich, the acupuncturist Dr. Wu, and chiropractor Dr. McCurdy. Pet. Exs. 40-41, 46-47, 61-66, 68-69, 71. On May 29, 2014, Dr. Strong recorded that B.A. was still having headaches, dystonia, and memory loss. A multiplanar, multisequence MRI with and without contrast of the brain, with a more powerful Tesla 3 scanner, was unremarkable. A repeat EEG on June 5, 2014 was also read as normal. Pet. Ex. 70 at 7.[15]

On June 23, 2014, B.A. went to Dr. H. Randall Griffith for a neuropsychological evaluation. Dr. Griffith observed severely impaired attention span; borderline/ low memory function; borderline/ low executive function, and mildly impaired overall cognitive severity. Pet. Ex. 73 at 5-6. He noted that Dr. Carter had previously concluded that B.A. had "variability in attention due to severe depression and anxiety, with no evidence of a cognitive disorder" and Dr. Carter also believed B.A. had a "pre-existing psychiatric disturbance" and then "experienced an extreme reaction to the onset of headache disorder." Pet. Ex. 73 at 7. Dr. Griffith saw less evidence of depression and anxiety. His impression was unspecified neurocognitive disorder, likely related to her psychiatric disorder as well as treatment with an anti-epileptic medication (Keppra). He wrote that it "appear[ed] plausible that [B.A.'s] catastrophic reaction to the [HPV vaccines] resulted in the onset of a somatoform disorder, which has evolved over time into conversion disorder." *Id.* at 8. He specified: "these conclusions are largely based on review of Dr. Carter's prior neuropsychological evaluation [in 2008] and reference to contemporaneous medical findings in that report, in conjunction with [B.A.'s] current clinical presentation and personality test results." Dr. Griffith suggested psychotherapy, pain management techniques, and cognitive exercises. Pet. Ex. 73 at 6-9.[16]

At the March 2016 entitlement hearing, her mother confirmed that B.A. continued to have severe headaches; muscle jerks; muscle pain; joint pain; short-term memory loss; and sensitivity to light, heat, and certain foods. Tr. 77-78. The mother presented clear and consistent testimony about B.A.'s medical history and explained how she and B.A.'s grandmother came to suspect that the vaccine may have played a role in the dramatic change in B.A.'s health after the second and third vaccinations.

B.A. did not testify. However, she sat in the gallery for most of the proceedings, over the course of two days. She missed only a portion of the afternoon of the first day because she became excessively fatigued. I focused on the witnesses testifying and counsel. However, I also observed B.A. while not making it apparent that I was doing so. It was clear to me that she had a

[15] This appointment with Dr. Strong and repeat imaging took place at least in part at my suggestion. Dr. Strong wrote: "She is here because the judge [in the HPV vaccine] case wants her to get more enhanced imaging to see if the technology in MRI is improved to see if we can find something to explain her complaints." Pet. Ex. 70 at 1.

[16] I also suggested this second neuropsychological evaluation. My order following the Rule 5 status conference on April 15, 2014, provided: "If petitioner intends to pursue a theory based on an injury that includes short term memory loss or other cognitive function, petitioner should consider obtaining an additional neuropsychological evaluation." Scheduling Order (ECF No. 80).

frequent, distinct facial tic or spasm in her cheek. This occurred throughout the proceedings, while she sat listening to the testimony.

V. Analysis

1. ADEM

i. Introduction

In this case, the parties vigorously disagreed as to the underlying nature or explanation for B.A.'s condition. She and her expert in neurology and immunology, Dr. Lawrence Steinman, offered an explanation of ADEM despite acknowledging that she was never diagnosed or treated for that condition. Respondent acknowledged that B.A.'s symptoms were well-documented. However, respondent argued that there was not preponderant evidence that she had ADEM, and therefore, Dr. Steinman's proposed theories are "wholly inapplicable" to this case. Resp. Version of Joint Pre-Hearing Submission at 2; Resp. Post-Hearing Brief at 3.

The Federal Circuit established the prevailing test for actual causation of an off-Table injury in *Althen*, 418 F.3d at 1278. In that case: "There was no dispute as to whether the petitioner, Margaret Althen, actually suffered from a central nervous system demyelinating disorder. Therefore, the Federal Circuit was not presented with a case in which the diagnosis itself was questioned, but one in which causation of the injury by the vaccine was the issue in dispute." *Doe v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 597, 611 (2010) (citing *Althen*, 418 F.3d at 1282), *aff'd, Lombardi v. Sec'y of Health & Human Servs.*, 656 F.3d 1343 (Fed. Cir. 2011).

Special masters are not tasked with specifically diagnosing injuries. In *Lombardi*, the Federal Circuit explained: "The function of a special master is not to 'diagnose' vaccine-related injuries, but instead to determine 'based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the petitioner's injury.'" *Lombardi*, 656 F.3d at 1343 (*citing Andreu*, 569 F.3d at 1382). Furthermore, neither the Vaccine Act nor *Althen* burdens petitioners alleging a non-Table injury to diagnose or categorize their injury – merely to show that the injury was caused by the vaccine(s) at issue. *Kelley v. Sec'y of Health & Human Servs.*, 68 Fed. Cl. 84, 100 (2005)

However, the Federal Circuit has determined that in certain instances, "if there is a dispute as to the nature of a petitioner's injury, the special master may opine on the nature of the petitioner's injury." *Contreras v. Sec'y of Health & Human Servs.*, 844 F.3d 1363, 1368 (Fed. Cir. 2017), *citing Hibbard v. Sec'y of Health & Human Servs.*, 698 F.3d 1355 (Fed. Cir. 2012); *see also Locane v. Sec'y of Health & Human Servs.*, 686 F.3d 1375 (Fed. Cir. 2012); *Lombardi*; *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339 (Fed. Cir. 2010)).

In *Hibbard*, the Federal Circuit reasoned: "If a special master can determine that a petitioner did not suffer the injury that she claims was caused by the vaccine, there is no reason why the special master should be required to undertake and answer the separate (and frequently more difficult) question whether there is a medical theory, supported by 'reputable medical or scientific explanation,' by which a vaccine can cause the kind of injury that the petitioner claims to have suffered." 698 F.3d at 1365.

The case law also suggests that while the special master is not required to reach a specific diagnosis, the special master may appropriately evaluate at least the nature of petitioner's injury and whether that aligns with petitioner's theory. For example, in *Broekelschen*, the petitioner's expert Dr. Steinman adopted certain treating physicians' diagnosis of transverse myelitis, a condition that is inflammatory in nature. Dr. Steinman then offered a causation opinion for that injury. Dr. Steinman did not offer a theory that would support other treating physicians' diagnosis of anterior spinal cord artery syndrome, which is *vascular* in nature. The Federal Circuit affirmed the special master's approach of first determining whether the petitioner's injury was inflammatory in nature before evaluating the theory of causation. 618 F.3d 1339, 1346.

In contrast, in *Contreras*, the Court of Federal Claims held that the special master erred by first evaluating whether the petitioner had transverse myelitis, Guillain-Barré syndrome, or both. The parties had agreed that because both of those injuries are inflammatory/ demyelinating in nature and had similar causes, the special master did not have to reach an exact diagnosis in order to assess causation. 107 Fed. Cl. 280, 288 (2012); *aff'd*, 844 F.3d 1363.

In this case, multiple facts are not disputed and are supported by the medical records, testimony, and my observations of B.A. To briefly restate the facts detailed earlier in this ruling, prior to receiving the HPV vaccinations at issue, B.A. experienced periodic headaches. These were associated with sinus infections, colds, and at least once looking at the computer for too long. These intermittent headaches were sufficient such that in 2003, when she was twelve years old, she underwent a brain CT scan which showed no structural abnormality. She did also have periodic medical visits for gastrointestinal complaints, sinus infections, and colds. But in general, she appeared to have been a healthy, successful, and active high school student as described above. In summer 2007, she served as a People to People student ambassador on a trip to several countries in Europe.

It is also undisputed that approximately one week after B.A. received the second HPV vaccine on January 23, 2008 (when she was sixteen years old), she developed severe, debilitating, and persistent headaches. These headaches did not correlate with visual strain, sinus infections, or colds. Indeed, severe headaches became the predominant symptom in her medical history. The symptoms continued, together with an array of secondary symptoms, for several months. These subsided somewhat, but then increased within about ten days of the third HPV vaccine on June 23, 2008 (when she was seventeen years old).

In addition to the headaches, B.A. developed other symptoms including sensitivity to light, sound, and movement; fatigue; insomnia; joint pain; muscle pain; tremors and muscle spasms. She also developed depression and anxiety, which were not present before and which she often attributed to the headaches and other symptoms.

She also suffered cognitive deficits. A comparison of her first neuropsychological evaluation in July 2008 and her second neuropsychological evaluation in 2014 reflects a significant decline in various cognitive functions including short-term memory, executive function, and concentration. *See* Pet. Ex. 5; Pet. Ex. 73. She missed considerable time from high school, although she did manage to graduate, partly by way of home schooling. She enrolled in college, funded partially by a merit-based scholarship. However, due to her symptoms, she was

unable to complete her assignments and had to drop out. She also developed a frequent facial tic or spasm in her cheek, which I personally observed during the entitlement hearing.

B.A. sought medical attention from various medical providers specializing in pediatrics, neurology, psychiatry, neuropsychology, otolaryngology, allergy, headache disorders, chiropractic, acupuncture, and other fields. Various tests – including MRIs, EEGs, and CSF analyses – were interpreted as normal. Her physicians did not consider or offer treatment appropriate for ADEM or another CNS inflammatory condition.

However, the physicians did not reach any other specific diagnosis. They did not suspect idiopathic intracranial hypertension (IIH) and the normal opening pressures on her cerebral spinal fluid taps appeared to rule that out. She was generally described as having a headache disorder. She was prescribed numerous medications over the time period in question, often in the general category of migraine medications. However, she has seemed to obtain temporary relief only through acupuncture from Dr. Wu, beginning in July 2010. Unfortunately, the theory of the treatment was not described at the hearing and it is unclear whether such information would have provided any clue to the nature of petitioner's injury.

I agree that petitioner bears the burden of establishing that she has the injury she asserts – ADEM, a CNS inflammatory condition - particularly when no treating physician has offered that assessment. As the Federal Circuit reasoned in *Hibbard*, if petitioner does not establish that she has this alleged injury, it would be impractical to evaluate a theory of vaccine causation that does not fit. Here, as in *Broekelschen*, petitioner's expert Dr. Steinman has theorized that the HPV vaccine caused an inflammatory response directed at the myelin basic protein at the blood-brain barrier. If there is not preponderant evidence that B.A. has suffered an injury of that nature, this theory would be inapplicable.[17]

ii. Association with Vaccines

Dr. Steinman opined that B.A. developed acute disseminated encephalomyelitis (ADEM) as a result of the HPV vaccines. Tr. 149; *see also* Pet. Ex. 59 at 1, 11.[18] ADEM has been defined as an "immune-mediated inflammatory disorder of the central nervous system that

[17] Petitioner cited a recent opinion by Chief Special Master Dorsey for the proposition that a unifying diagnosis is not needed. Pet. Post-Hearing Brief at 9, *citing Harmon v. Sec'y of Health & Human Servs.*, No. 12-298V, 2017 WL 2872293 (Fed. Cl. Spec. Mstr. June 6, 2017). In *Harmon*, the treating physicians suspected various conditions including a cerebrovascular event, aneurysm, CNS vasculitis, ADEM, and various forms of multiple sclerosis. They treated for multiple sclerosis. While their experts debated the diagnosis, the parties stipulated that the petitioner "suffered from a CNS inflammatory demyelinating disease." *Harmon* at *21. Accordingly, the chief special master reasoned that it was not necessary to determine a precise diagnosis. *Id.*

[18] It should be noted that Dr. Steinman raised a second theory to explain how the HPV vaccine can cause headaches. Briefly, he opined that the HPV vaccine contains alum, an adjuvant which enhances the immune response to the vaccine antigens. He theorized that the alum triggers inflammatory mediators present in the trigeminal ganglion, which innervates the meninges and blood vessels in the brain and thus could explain the severe headaches. This theory would not necessarily involve ADEM. Tr. 290. It will be discussed below.

commonly occurs within one month from antigenic challenge."[19] Cases of ADEM have been associated with infections and with vaccines, including HPV vaccine. Pet. Ex. 107 at 1-2.

Dr. Steinman's opinion was informed by his expertise and evaluation of the facts in this case. He also relied on changes made to the HPV vaccine package insert. The 2009 edition[20] listed headaches as the most commonly reported adverse event. Pet. Ex. 118 at 6. It also listed headaches in a list of nervous system disorders reported during post-marketing surveillance. *Id.* at 9. In 2011, the package insert[21] was amended to also list headaches as a *serious* adverse event. Pet. Ex. 94 at 7. Headaches were categorized as a nervous system disorder. *Id.* ADEM was also added to the top of the same list of nervous system disorders. *Id.* at 11[22]; Tr. 125-26. In response to my question, Dr. Steinman opined that it was hard to tell whether these changes to the package insert constituted a signal. Although, he did not know the actual volume of reported incidence of headaches and ADEM, he felt that their occurrences were significant based on their prominent placement in the package insert. Tr. 161-62.

iii. Symptoms

Dr. Steinman found the key symptom in this case to be B.A.'s severe chronic headache. He opined that this can be caused by ADEM, which involves inflammation at or near the blood vessels in the white matter at the blood-brain barrier. Dr. Steinman opined that most of his colleagues in neurology would agree that an intense inflammatory reaction at the blood-brain barrier can cause chronic headaches. Tr. 249-50. Dr. Steinman opined that B.A.'s observable facial tic could also be attributed to an inflammatory CNS condition including ADEM. He opined that facial tics stem from the junction of the central and the peripheral nervous systems. Facial tics are frequently seen in multiple sclerosis (another condition on the same spectrum as ADEM). Tr. 565. Dr. Steinman believed, based on B.A.'s general restlessness and moving around during the hearing, that she had akathisia. Tr. 562. He also viewed her fatigue, decreased activity, weight gain, eye pain, light hypersensitivity, ringing in ears, nausea, vomiting, abdominal pain, back pain, dizziness, cold intolerance, depression, anxiety, and memory loss as consistent with or secondary to ADEM. These symptoms could also be consistent with brain infections such as meningitis or encephalitis, but there was no evidence of those in this case. Tr. 115-24; *see also* Pet. Ex. 74 at 23; Pet. Ex. 89 at 2. Dr. Steinman opined that B.A.'s headaches, personality change, focal neurological symptoms, and lethargy could

[19] Pellegrino et al., *Acute Disseminated Encephalomyelitis Onset: Based on Vaccine Adverse Events Reporting Systems*, PLoS One (2013); doi: 10.1371/annotation/1d544202-04f5-4848-83f1-696c2de4221e [Pet. Ex 107] at 2.

[20] Merck & Co., *Gardasil Package Insert* (revised June 2009) [Pet. Ex. 118].

[21] Merck & Co., *Gardasil Package Insert* (revised April 2011) [Pet. Ex. 94].

[22] *See also* Merck & Co., *Gardasil Package Insert* (revised April 2015) [Pet. Ex. 119] (continuing to list these same adverse events).

constitute an encephalopathy, which is listed among the clinical signs of ADEM by the Brighton Group (discussed further below).[23] Tr. 117-18.

After discussing all of these matters, Dr. Steinman admitted that B.A. had a host of symptoms and it was difficult to say whether ADEM was a unifying diagnosis for all of them. Tr. 549-50. However, he thought that ADEM explained the most.

Dr. Steinman stated that in his clinical experience, 20% of the time, he diagnoses and begins treatment for ADEM based on the clinical neurological exam, the clinical picture, and ruling out alternate conditions without positive MRI or CSF evidence. Tr. 108, 114.

In his reports, respondent's expert Dr. Leist did not particularly address whether B.A.'s post-vaccination symptoms were consistent with ADEM. Resp. Exs. A, I. At the hearing, Dr. Leist stated that B.A. had experienced periodic headaches in years prior to the events in this case. However, he agreed that there was significant evidence that B.A. experienced a significant change in the severity and nature of her headaches beginning approximately ten days after the January 23, 2008 HPV vaccination that went on over time. However, apart from the mother's testimony, he did not see clear evidence that B.A. experienced a lower plateau, followed by a bump up in headaches shortly after the July 2008 HPV vaccination. Tr. 345.

Dr. Leist acknowledged that severe headaches, fatigue, nausea, vomiting, and photophobia were all recognized symptoms of ADEM. However, each of these symptoms is very non-specific and consistent with many other conditions as well. Tr. 322-25.

Dr. Leist disagreed that B.A. developed encephalopathy. He defined encephalopathy as a decreased consciousness or awareness, which prevents the person from performing daily functions and interacting appropriately with one's surroundings. Tr. 322-23. He opined that B.A.'s awareness and functioning did not decrease, rather they increased. He pointed to the mother's testimony as well as records dating back to July 2008 to suggest that B.A. had increased sensitivity to light and sound, such that she could hear the pages of a book turning in a separate room. Tr. 325-26, *citing, e.g.*, Pet. Exs. 5, 9; Tr. 21.[24] After the hearing, I reviewed the Brighton group's article. In contrast to Dr. Leist's statement that encephalopathy can involve only *decreased* awareness, the Brighton group recognizes "sensory abnormalities (either *positive* or negative sensory level)." Resp. Ex. J at 5777-79 (emphasis added).

Like Dr. Steinman, Dr. Leist often sees patients with suspected ADEM in his clinical practice. Tr. 314. He indicated that he sometimes makes an initial diagnosis and begins treatment for ADEM without having objective evidence. But he said that over the course of treating a patient, he tends to acquire additional data and refines the diagnosis. He would want to

[23] Sejvar J.J. et al., *Encephalitis, Myelitis, and Acute Disseminated Encephalomyelitis (ADEM): Case Definitions and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data*, 25 Vaccine 5771 (2007) [Resp. Ex. J].

[24] It should be noted that B.A. did have significant issues with performing her daily functions when suffering from the headaches in that she missed months of school and had to drop out of college secondary to the headache pain.

see additional data more clearly traceable to the central nervous system before ADEM would rise to the top. Tr. 321-25.

iv. MRIs

The experts agreed that no demyelination was found on B.A.'s five brain MRIs, conducted on February 4, 2008; January 20, 2009; April 16, 2009; October 11, 2011; and June 5, 2014.[25] *See, e.g.*, Pet. Ex. 59 at 1; Tr. 271-72.

Dr. Steinman recognized that ADEM is often if not usually associated with demyelination. However, he submitted an article by Höllinger et al.[26] for the proposition that patients with ADEM can have negative findings on MRIs and other objective tests. Pet. Ex. 74 at 2. This was a study of ten patients (ranging from 27-62 years old) who had preceding viral infections, then developed various neurological symptoms including fever, nausea, fatigue, disorientation, headache, tetraparesis, seizures, and coma. They were treated with corticosteroids, antiviral therapy, plasma exchange, and/ or intravenous immunoglobulin ("IVIG"). They were followed for 8 to 48 months (median time 30 months). Pet. Ex. 75 at 1.

Höllinger et al. reported that 10 / 10 ADEM patients underwent MRIs and 9 / 10 repeated it at least once. However, 50% of patients showed only "subtle" abnormal findings on MRI. The other 50% had normal findings. Thus, Höllinger et al. opined that "MRI should not be relied upon when defining a diagnosis of ADEM." Pet. Ex. 75 at 327. They also stated that "MRI findings frequently are normal even with a severe clinical picture and should not be considered a diagnostic prerequisite." *Id.* at 328.

Dr. Steinman therefore opined that the absence of objective evidence such as MRI findings in ADEM cases is "not unusual," so he was "not overly concerned about this lack of objective evidence in [B.A.'s] case." Pet. Ex. 74 at 2. However, upon review of the article, I note that Höllinger acknowledges that many recent large studies have used MRI findings to confirm ADEM and to "[the authors'] knowledge, the possibility of normal MRI findings in ADEM during the whole disease course has not yet been reported." Pet. Ex. 75 at 321.

While Höllinger's group followed their patients for a median of 30 months, their follow up MRIs were not as far out. The study included only 10 patients, 5 of whom had normal MRI findings. In 4 of those patients, the repeat normal MRIs were only 1 - 2 weeks after the presentation of neurological symptoms. Pet. Ex. 75 at 322. Only 1 patient had a repeat normal MRI significantly later on – at 270 days, nearly a year afterwards. *Id.* Dr. Steinman is correct that half of the patients had no positive findings on repeat MRIs. However, the study would have been more persuasive if it were more robust and if more than one patient had negative findings more than two weeks after onset.

[25] The brain MRIs have been previously cited, but for ease of reference, they are located at Pet. Ex. 24 at 8-9; Pet. Ex. 10 at 14; Pet. Ex. 28 at 91; Pet. Ex. 34 at 5; Pet. Ex. 41 at 1.

[26] Höllinger P et al., *Acute Disseminated Encephalomyelitis in Adults: A Reappraisal of Clinical, CSF, EEG, and MRI Findings*, 249 J. Neurol. 320 (2002) [Pet. Ex. 75].

Dr. Leist opined that sometimes a patient's first MRI will not show abnormalities. Tr. 322. However, "[s]ome, the majority of them have abnormalities on later findings." Tr. 314, 321-22. He said it would be highly unlikely that a patient would go through a course of ADEM and never have objective MRI results. Tr. 322.

Dr. Leist also discussed an article from a group of authors from the United States, Holland, Jordan, Switzerland, and Finland, called the Brighton Collaboration Encephalitis/ ADEM Working Group ("the Brighton Group"). They proposed standardized criteria with varying levels of diagnostic certainty. Resp. Ex. J at 5771. Dr. Leist briefly concluded that B.A. did not qualify at any level of diagnostic certainty for ADEM. Resp. Ex. I at 8; *see also* Tr. 320. Dr. Steinman stated that he does not use the Brighton Group's criteria because he finds them too rigid. He also found the criteria difficult to follow because of the various footnotes and definitions. However, he is familiar with the Brighton group criteria. He stated that it described many of the symptoms experienced by B.A., thereby supporting his opinion in this case. Tr. 109-18, 149-50,191-92, 232, 237.

In their preamble, the Brighton Group state: "The diagnostic hallmark of ADEM is the demonstration of scattered, focal or multifocal (disseminated) areas of inflammation and demyelination within cerebral subcortical and deep cortical white matter." Resp. Ex. J at 5775. "While these lesions may be demonstrable by histopathology, it is far more likely that MRI will be the diagnostic modality by which the diagnosis is made." *Id.* The Brighton Group's first and second levels of diagnostic certainty require MRI findings displaying diffuse or multifocal white matter lesions on T2 weighted, diffusion weighted, or FLAIR sequences on T2 weighted imaging. *Id.* at 5778-79. I agree that because B.A. had no positive findings on MRI, she would not qualify for the diagnosis at these levels.

However, the third level does not require positive MRI findings. The inclusion criteria are one or more "focal or multifocal findings referable to the central nervous system," which include encephalopathy and sensory abnormalities. Resp. Ex. J at 5779. The exclusion criteria for the third level (and the others) are: "presence of a clear alternative acute infection or other diagnosis for illness; recurrence or relapse of illness at any point following a 3 month period of clinical improvement from symptomatic nadir; or if known, MRI findings or histopathologic data inconsistent with the diagnosis of ADEM." *Id.* Dr. Steinman opined that B.A. had one or more of the inclusion criteria (abnormal sensory levels and possible encephalopathy) and none of the exclusion criteria, allowing a diagnosis of ADEM at the third level.

I agree that B.A. seems to have many of the symptoms of ADEM as described by the Brighton Group. She seems to meet the inclusion criteria for the third level of diagnostic certainty. However, the Brighton Group created the lower levels of diagnostic certainty "to achieve sufficient specificity even in the absence of resource-intensive diagnostic methods." *Id.* at 5572. That certainly does not describe the present case, as B.A. underwent multiple MRIs, including the more sensitive 3T MRI, all of which were normal.[27]

[27] In cases in which MRIs or other scans of the central nervous system are at issue, counsel should obtain the films and consider having them re-read by an expert neuro-radiologist, as subtle findings are often missed particularly when general symptoms like headaches are at issue.

The Brighton Group states that MRI findings are the "diagnostic hallmark" of ADEM. *Id.* at 5771. And as noted above, their exclusion criteria include MRI findings inconsistent with the diagnosis of ADEM. *Id.* at 5779. I question whether repeated normal MRI findings over a course of several years while the individual remains symptomatic are in fact inconsistent with ADEM. Thus, the Brighton Group does not particularly support a finding of ADEM in this case.

v. EEGs

Höllinger et al. noted that even before the advent of MRIs, EEGs were recognized as an important diagnostic tool for ADEM. Pet. Ex. 75 at 321. In their study, 8 subjects underwent EEGs, 7 of whom had abnormal findings which varied greatly ranging from signs of increased sleepiness, to mild generalized slowing, to severe generalized slowing. *Id.* at 323. Positive EEG findings were "particularly important to prove the organic nature of disease" in two young females who were "initially suspected of suffering from a psychiatric disease" and had normal MRIs. *Id.* Höllinger et al. also observed: "The degree of abnormality in the EEG correlated well with clinical symptoms." *Id.* at 327. Thus, they contended that EEGs were "of utmost importance" in determining CNS dysfunction. *Id.* They concluded that "EEG is of greatest help in proving encephalopathy and best correlates with the clinical course." *Id.* at 328.

At the hearing, Dr. Leist acknowledged all of these findings and conclusions by Höllinger regarding EEGs. He saw no reason to disagree with them. Tr. 271. Dr. Leist also opined that in the ADEM patients he sees, "most" have EEG abnormalities. Tr. 321-22.

The Brighton group's criteria for ADEM does not specifically include positive EEG findings. However, they also include criteria for encephalitis, which do include EEG findings such as "diffuse or multifocal nonspecific non-physiologic background slowing." Resp. Ex. J at 5777, n. 8. They also state that the markers of inflammation (including EEG) for acute encephalitis are the same as for ADEM. *Id.* at 5775.

In the present case, B.A. underwent two EEGs. Dr. Steinman testified that he believed these were normal, but he would need to check. Tr. 272, 563. Dr. Leist opined that B.A.'s EEGs were normal. Tr. 350, 373. Upon my subsequent review, both EEGs were read as normal. The June 5, 2014 EEG, with B.A. in a state of wakefulness and "some" drowsiness, displayed no abnormalities. Pet. Ex. 70 at 7. However, the February 19, 2008 EEG - performed while B.A. was awake, drowsy, and asleep - displayed generalized slowing on the drowsy record. Pet. Ex. 3 at 12. The literature suggests that EEGs are an important diagnostic tool for ADEM. But in this case, the treating physicians treated B.A.'s two EEGs as normal and the experts did not rebut that finding. Thus, I cannot conclude that the EEGs are supportive of ADEM.

To be sure, the assessment that B.A. developed ADEM would be much more compelling if at least some of the objective findings were suggestive of ADEM. If I read the Höllinger et al. article as liberally as Dr. Steinman does, B.A.'s MRI and EEG findings do not rule out ADEM but they make it more difficult to rule it in. However, upon considering that 4 / 5 patients with normal MRIs only had follow-up MRIs within 2 weeks of onset and that 7 / 10 patients had abnormal EEGs, it is difficult to conclude that B.A. had ADEM when all of these studies were negative in her case.

vi. Cerebrospinal Fluid (CSF) Findings

Dr. Steinman opined that apart from B.A.'s symptoms, the best evidence of ADEM was her March 10, 2008 cerebral spinal fluid finding of elevated protein.

Höllinger et al. state that CSF results are another recognized diagnostic tool for ADEM. Pet. Ex. 75 at 321. All 10 of their patients had CSF findings for evaluation. 50% were normal and the other 50% were mildly abnormal, particularly showing mild pleocytosis with predominantly mononuclear cells (ranging from 13 – 22 cells / mL) and protein of 0.7 g/l or less. Pet. Ex. 75 at 323. Höllinger et al. stated: "Assessment of CSF is important to diagnose an infectious disease. Normal findings, however, do not exclude an inflammatory or antibody-mediated CNS affection." *Id.* at 327. The Brighton group wrote that pleocytosis[28] is "the most reliable indicator of CNS inflammation," though they did not list it among the criteria for ADEM. Resp. Ex. J at 5774, 5778-79.

Dr. Steinman initially wrote that B.A.'s CSF findings were also normal. Pet. Ex. 59 at 3; Pet. Ex. 74 at 1. He was relying on the treating physicians' descriptions. Tr. 104. While preparing for the hearing, Dr. Steinman reviewed the lab report from the March 10, 2008 CSF analysis. *See* Pet. Ex. 31 at 13-16, 26-27, Pet. Ex. 9 at 8, 11. He observed that B.A.'s protein level was 49 mg/dL. The reference range was 15 – 45 mg/dL. This result *appeared* only slightly elevated. However, Dr. Steinman submitted a study by Wong et al.[29] to demonstrate that for subjects from ages 14-18, the mean value for CSF protein was 26 mg/dL and the normal range was 23 – 29 mg/dL. B.A. was 16 years old in 2008, when she was found to have a protein level of 49 mg/dL. Thus, her protein level was well above the 90th percentile for her age group. Dr. Steinman stated that this was objective evidence of an inflammatory process and the strongest evidence that B.A. had ADEM. *See, e.g.*, Tr. 99-101; Tr. 564-65. Dr. Steinman noted that on March 10, 2008, the same lumbar puncture also yielded a gram stain with rare white blood cells. Dr. Steinman opined that these white blood cells were additional evidence of an inflammatory process such as ADEM. Tr. 105-06.

Dr. Leist disagreed that B.A.'s March 10, 2008 CSF analysis was supportive of ADEM. He acknowledged that the CSF protein level was "marginally increased over what would be the upper limit of normal." Tr. 305. However, he opined that this was the result of a "traumatic tap." In other words, the lumbar puncture allowed blood to enter the CSF. He noted that the CSF not only contained trace white blood cells, but 770 red blood cells. *See* Pet. Ex. 31 at 16. Dr. Leist opined that these blood cells explained the elevated CSF protein level. Tr. 305-14, 382-83.

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[28] Pleocytosis is the "presence of a greater than normal number of cells in the cerebrospinal fluid." Dorland's Illustrated Medical Dictionary (32nd ed. 2012) (hereinafter "Dorland's") at 1460. *See also* Adams and Victor's Principles of Neurology (10th ed. 2014) at 939 (stating that in cases of ADEM: "The CSF shows a slight increase in lymphocytes and protein content, but these are highly variable, with a few of our patients having only an increase in protein and no cells and others having up to several hundred cells.").

[29] Wong M. et al., *Cerebrospinal Fluid Protein Concentration in Pediatric Patients: Defining Clinically Relevant Reference Values*, 154 Arch. Pediatr. Adolesc. Med. 827 (2000) [Pet. Ex. 124].

Dr. Leist noted that Wong et al. automatically excluded patients who had a traumatic lumbar puncture, defined as either "(1) the report of blood in the CSF sample by the physician in the procedure note or by the laboratory, or (2) more than 200 x 10^6 erythrocytes [red blood cells] per liter in the leukocyte count." Pet. Ex. 124 at 2. Dr. Leist opined that because B.A.'s CSF sample contained blood, it would have been excluded from the Wong study. Tr. 306-07.

Dr. Steinman opined that Wong et al. may have excluded any CSF sample with more than 200 red blood cells because they wanted only samples that were "pristine." He believed that B.A.'s CSF sample with 770 red blood cells was not "pristine," but it was only "a little bit traumatic." A truly traumatic tap would be "a hundred thousand or a million" red blood cells. Tr. 388. Dr. Steinman further opined that the number of red blood cells did not explain the "significantly" elevated protein level. He cited an article by Seehusen et al.[30] for the proposition that for every 1,000 red blood cells per MM^3 present, 1 mg/dL of protein should be subtracted. Pet. Ex. 125 at 4. Because B.A.'s sample contained 770 red blood cells, the CSF protein level should be adjusted from 49 to 48 mg/dL. This was still well above the 90th percentile for a 14 to 18-year-old subject. Tr. 387-90, 566-69. Dr. Steinman testified that he and his colleagues at Stanford used essentially the same methodology while treating patients. Tr. 390.

I find that Dr. Steinman persuasively explained that the treating physicians may have viewed B.A.'s protein level as being only mildly elevated. Based on the Wong article, better practice would have been to adjust the reference range for her age group. There may have also been an assumption that B.A.'s elevated protein was due to a traumatic tap. However, Dr. Steinman showed that under Seehusen et al.'s algorithm, 770 red blood cells from a traumatic tap would elevate the protein level only slightly. Even when that was accounted for, B.A.'s protein level would be 48 mg/dL, still significantly above the reference range for her age group (23 – 29 mg/dL) and still above the range for adults (15 – 45 mg/dL). Thus, the March 10, 2008 CSF protein level offers support for a CNS inflammatory process.

The experts also discussed the second CSF analysis which occurred at the Diamond Headache Clinic on April 17, 2009. B.A. was still quite symptomatic. She had, of course, not received any treatment for ADEM such as IVIG or corticosteroids. However, her CSF was 22 mg/dL, well within the normal range for adults (and slightly below the range for adolescents offered by Wong et al.). Her opening pressure was again normal. Dr. Steinman acknowledged that this raised an issue: if the elevated CSF protein represented an inflammatory process, how did that "normalize" while her symptoms were still "raging"? He acknowledged that this was a confounder even while it reinforced the notion that the 49 level on the earlier test was significantly abnormal. Tr. 105. However, this did not change his opinion that the first elevated protein level was a significant finding in B.A.'s medical work-up.

vii. Diagnosis by Treating Physicians

In this case, B.A. was seen on multiple occasions by four different neurologists – Dr. Gehi, Dr. Valero, Dr. Strong, and Dr. Diamond. Pet. Exs. 4, 9, 13, 31. None of them even listed ADEM on their differential diagnosis.

[30] Seehusen D. et al., *Cerebrospinal Fluid Analysis*, 68 Am. Fam. Physician 1103 (2003) [Pet. Ex. 125].

Dr. Leist opined this was because B.A. had no objective findings on MRI or EEG, and the elevated CSF protein level was attributed to a traumatic tap. As noted above, I agree with Dr. Steinman that the protein level was significantly elevated even if the tap was viewed to be traumatic. Dr. Steinman opined that if the treating physicians had connected the elevated protein level with some of her non-specific symptoms (e.g., headaches), they might have suspected and treated for ADEM. However, the treating physicians did not make this connection. Tr. 274-76, 287.

Dr. Steinman also noted that in 2008, when B.A. received the HPV vaccines at issue and suffered the onset of these symptoms, the vaccine had not been around long and the package insert did not list headaches and ADEM as serious adverse events. Dr. Steinman suggested that if the treating physicians were aware earlier of a possible link between the HPV vaccine, headaches, and ADEM, they may have considered ADEM in B.A.'s case. Tr. 274-77.

Dr. Steinman is correct that ADEM did not appear as a serious adverse event in the package insert until 2011 based on post-licensure experience. However, several treating physicians were aware that B.A. and her mother believed that the HPV vaccine was causing her symptoms and they could have drawn the connection once the package insert was updated. First, Dr. Ulrich, who took over as her family physician in June 2009, Pet. Ex. 40 at 11, continued to see her frequently mostly for severe headaches and dystonic movements in the head and face. He recorded that onset was shortly after the HPV vaccination. His 2010 letter to B.A.'s college provides that she had a reaction to the HPV vaccine. He also recorded at that time, that B.A. was under a lot of stress and her headaches had gotten worse. While it does seem that he accepted the history as provided by B.A. and her mother, he did not do any particular diagnostic work-up that would have shed additional light on the connection to the vaccine and did not make a diagnosis of ADEM.

Additionally, in 2014, neurologist Dr. Strong ordered a 3T MRI, noting that the judge adjudicating B.A.'s vaccine claim wanted to know whether the stronger magnet would detect anything that the prior scans had not. Pet. Ex. 70 at 1. He never raised the possibility of ADEM.

I recognize that the treating physicians did not suspect ADEM in B.A.'s case. I do not fault them for not considering this particular explanation in this complex case particularly when none of the hallmark signs of ADEM was present as discussed above. But equally important, I note that they did not come to any other unifying diagnosis to explain the severe headaches and other symptoms nor the history of the disease process. I do not tend to see this as strong evidence for or against a conclusion of ADEM.

viii. Treatment and Clinical Course

Höllinger et al. provide that ADEM "typically runs a monophasic course with a large variation as to disease duration and extent of recovery." Pet. Ex. 75 at 321. "However, recurrent episodes of ADEM were repeatedly claimed to exist." *Id.*

The Brighton Group provides that ADEM is "monophasic." Resp. Ex. J at 5775. Their diagnosis of ADEM (at any level of certainty) excludes a finding of "recurrence or relapse of illness at any point following a three-month period of clinical improvement from symptomatic

nadir." *Id.* at 5779. The preamble to the criteria explains "that it has been recognized, however, that in some cases of ADEM, the premature cessation or tapering of therapy (e.g. corticosteroids) may lead to a recurrence of symptoms. For this reason, the monophasic nature of ADEM will be defined as a lack of recurrence (within 3 months) in the absence of treatment or *while on appropriate treatment*. Relapse occurring during cessation or tapering of therapy should be considered to belong to one monophasic episode." *Id.* at 5775 (emphasis added). The evidence seems equivocal as to whether every patient gets better within a relatively short time frame. However, most diagnoses of ADEM are converted to MS upon a finding of new lesions.

Dr. Steinman opined that B.A.'s symptoms (e.g., the headaches, photophobia, light sensitivity, and sound sensitivity) had an acute onset. He acknowledged the symptoms have not gone away, which is anomalous for ADEM. Tr. 390. But he also suggested that if she had received the appropriate treatment for ADEM (IVIG, steroids, and/ or plasmapheresis), she may have gotten better. Tr. 274-76, 287.[31]

Dr. Leist opined that ADEM generally has an acute onset followed by recovery. Tr. 320. He opined that a prolonged course of ADEM is possible, but would be associated with observable brain atrophy, which was not seen in B.A.'s case, at least at the last MRI on June 14, 2014. Tr. 361. Dr. Steinman responded that he has seen a lot of pediatric patients, and they do not tend to develop atrophy. That is more likely in adults. Tr. 566.

I do not see clear evidence that B.A.'s symptoms ever ceased for at least three months and then recurred, although they did seem to be worse at some times than at others. If she does have ADEM, the course seems unusually long. However, she never received appropriate treatment for ADEM.

Dr. Steinman opined that he would still present B.A. as a case of ADEM to his colleagues at Stanford University during grand rounds. However, he admitted that "it would be a lot easier if everything added up." Tr. 565. Dr. Leist maintained that in the absence of specific findings beyond the CSF abnormality, he could not make that diagnosis and at most could maintain it as a potential rule out without objective findings. Tr. 322.

ix. Conclusion

It is difficult to accept Dr. Steinman's opinion that B.A. developed ADEM. There is compelling evidence that B.A. did develop severe, chronic headaches and other new symptoms after the January 23, 2008 HPV vaccine. Her treating physicians consistently recorded these symptoms, particularly the headaches. They have not settled on any overarching diagnosis.

[31] Both experts noted the testimony of B.A.'s mother to the effect that acupuncture administered by a particular acupuncturist did provide some temporary relief, but neither professed to understand enough about eastern medicine to explain how that treatment could have provided relief. In any event there was no evidence that the acupuncture relieved the symptoms for three months.

Dr. Steinman proposed a diagnosis of ADEM. This condition has been associated with infections and vaccines including the HPV vaccine. Indeed, the package insert now discloses reports of ADEM following the HPV vaccine. The package insert also lists severe headaches among the most common and serious adverse events reported. The literature and both parties' experts agreed that headaches and many of the other symptoms experienced by B.A. are consistent with ADEM. However, each symptom is quite non-specific. Additionally, Dr. Steinman admitted that it was difficult to present a unifying diagnosis for *all* of her symptoms. Tr. 549-50.

Dr. Steinman stated that there was a "lack of objective evidence in this case" for ADEM, but that was not unusual and not overly concerning. Pet. Ex. 74 at 2. While the experts agreed that ADEM can present with a normal MRI, Dr. Leist testified that it would be highly unlikely for the condition to continue for a prolonged course, as in this case, with no objective findings on MRI or EEG. The literature submitted in this case indicates that MRI findings are the diagnostic hallmark of ADEM even if not present in all cases. Resp. Ex. J at 5775. Indeed, Höllinger recognizes this focus on MRI findings. While Höllinger reports on 5 patients with normal MRIs, those generally were not repeated beyond a two-week period. Pet. Ex. 75 at 323 (showing that only 1 patient had a normal repeat MRI more than 2 weeks after onset). It is certainly unusual that B.A. underwent five MRIs, including one with a 3T magnet more than 6 years after onset, with no MRI findings suggestive of ADEM. EEGs are also helpful to diagnosing ADEM, but not in this case. B.A.'s two EEGs were read as normal. I agree with Dr. Steinman that B.A.'s first CSF protein was significantly elevated. However, to the extent that is supportive of ADEM, it is undercut by the protein level inexplicably going back down to normal while her symptoms were "still raging." Indeed, her clinical course seems unusually long for ADEM. It is possible that proper treatment for ADEM would have helped. However, that relates back to the puzzling lack of objective findings. One would think that as the condition persisted, it would be more likely to result in at least some objective findings if indeed she had ADEM. I also agree that the treating physicians were, at least initially, unaware of a possible association between the HPV vaccine and ADEM. However, I am not sure that carries much weight. Even if they were aware of that association, B.A.'s case certainly would not constitute a classic case of ADEM and I am not sure that diagnosis would be made.

I appreciate both experts' discussion of the facts, their clinical experience, and the literature. However, for the reasons discussed above, I cannot conclude that the evidence shows more likely than not that B.A.'s symptoms were manifestations of ADEM.

2. Headache Disorders

In this case, there is not preponderant evidence of ADEM but there is a compelling temporal association between the HPV vaccines and B.A.'s symptoms, most predominantly the chronic severe headaches.

The difficulty is that the causal diagnosis of headaches is very often particularly elusive. In retrospect, it would have been more helpful for the parties to offer further explanation of headaches more generally, rather than focusing on B.A.'s case and the likelihood of ADEM. My understanding, based on my prior experience with complex tort claims including carbon monoxide injuries and trauma and my review of the literature, is that headaches have various

presentations. Some, such as the sinus headaches B.A. suffered occasionally prior to her vaccinations, can generally be diagnosed fairly easily because of their location and their association with viral infections and allergies. Cluster headaches have a common pattern not present in this case. Migraines can have classical symptoms but often do not. Dr. Leist suggested that patients with chronic migraines sometimes have similar symptoms to those experienced by B.A. and others do not. Tr. 326. Symptoms or triggers have been described as being more typical of migraines, cluster headaches, and tension headaches. Often these are not consistently present to explain the headaches and the underlying cause is often not known. The cause of headaches often is attributed to a particular trigger such as certain foods with migraines, or tension or menstrual cycles but the reason therefore is generally not well understood.[32] Severe headaches such as those resulting from carbon monoxide exposure are often misdiagnosed as migraines with the term seemingly being used synonymously with bad headache. It does appear that headaches can be explained with a variety of theories.

Additionally, in this case, the treating physicians' overriding assessment was that B.A. had a headache disorder. She traveled from Alabama to Illinois to seek treatment at the renowned Diamond Headache Clinic. After conducting comprehensive in-patient testing and treatment, Dr. Merle Diamond recognized the severity of B.A.'s headaches. However, they were not noted to be in a particular category (migraines, tension, cluster, etc.). She has received multiple different treatments and medications over the course of the years during which she suffered with the headaches.

Petitioner has submitted literature regarding the HPV vaccine and headaches which do not depend on a diagnosis of ADEM. Her expert Dr. Steinman offered a second theory involving the antigen and the alum in the vaccine, which he said could stand independently from the ADEM theory. I will address this remaining evidence below.

3. Headaches and HPV

Dr. Steinman opined that it was significant that the HPV vaccine package insert lists that the most common side effect is headaches. Headaches are also on the list of serious side effects. Pet. Ex. 118 at 6; Pet. Ex. 94 at 7. As I have rejected Dr. Steinman's opinion that B.A.'s headaches and other symptoms represent ADEM, it remains to be determined whether he has presented a sound and reliable theory to explain the severe headaches and associated symptoms that she suffered and which appear to be at least a somewhat frequently reported sequelae of the HPV vaccinations.

Petitioner cited at least two studies of HPV vaccines associated with severe headaches and many of the other symptoms which B.A. experienced. First, Brinth et al.[33] reported that since the introduction of the HPV vaccine in Denmark in 2006, "a collection of symptoms has been described that does not readily fit into an existing diagnostic entity." Pet. Ex. 92 at 1. Brinth's group, which practiced at a Danish hospital's Syncope Unit, described a group of

[32] *See generally* Diamond S., Diagnosing and Managing Headaches (2nd ed. 1998).

[33] Brinth, L. et al., *Suspected Side Effects to the Quadrivalent Human Papilloma Vaccine*, 62 Dan. Med. J. 1-5 (2015) [Pet. Ex. 92].

patients who had received HPV vaccines and were referred for a tilt-table test and evaluation of autonomic nervous system function. *Id.* After they excluded patients with pre-existing chronic disease and other possible eliciting factors, there were 53 young women (ranging in age from 12 – 39 years, mean age 21 years) who received the HPV vaccination within two months of symptom onset. *Id.* at 1-2. Most notably, 100% of the patients reported "new onset headache." *Id.* at 2. "Most of the patients described continuous, daily, severe, debilitating headache with intermittent exacerbations and occasionally pain-free periods. Only a few patients described typical migraines." *Id.* Additionally, 96% of the patients reported excessive fatigue (both mental and physical). *Id.* 89% reported cognitive dysfunction including inability to concentrate, impairment of short-term memory, diminished attention span, and "mental fog." *Id.* 66% reported involuntary muscle activity in the form of intermittent tremors and myoclonic twitches. *Id.* at 2-3. Also reported were disordered sleep (85%), light hypersensitivity, (70%) intermittent blurred vision (83%), menstrual irregularity (48%), and neuropathic pain (66%). *Id.* These symptoms are highly similar to the symptoms reported by B.A. *See, e.g.*, Pet. Ex. 43 at 1-5 (neurologist Dr. Strong's record from October 2011); Tr. 77-78 (mother's testimony). Brinth's patients also reported other symptoms which are less prominent in B.A.'s case. Those other symptoms were not reported with the same regularity as severe headaches. Brinth wrote that these symptoms "may at first seem both diffuse and very common." Pet. Ex. 92 at 4. However, Brinth stated that they had identified a recognizable pattern of symptoms with a close temporal association to HPV vaccination. *Id.* at 4. Brinth proposed that this constellation of symptoms could be due to dysfunction in the autonomic nervous system which innervates, monitors, and controls most tissues and organs in the body. *Id.* They suspected that this dysfunction is secondary to HPV vaccination and they said that further research was urgently warranted in order to clarify the pathophysiology. *Id.*

As noted by Brinth, in a separate study in Japan, Kinoshita et al.[34] reported on a very similar cohort of 40 young female patients (ranging in age from 11 – 17 years) who received HPV vaccines. After vaccination, Kinoshita's patients reported a range of symptoms including headaches (70%); general fatigue (53%); and decreased ability to learn (43%); arthralgias; pain and coldness in the legs and menstrual irregularity. Kinoshita et al. also theorized that these symptoms may represent an autonomic neuropathy with an autoimmune etiology. Pet. Ex. 93 at 2198-99. These studies reflect that a small but significant number of patients have experienced a similar complex of symptoms led by severe, chronic headaches following HPV vaccination as B.A. did. Both authors indicated that the phenomena reported in their studies warrants further study as to the underlying cause.

At the hearing, I asked Dr. Steinman why he did not consider whether B.A.'s severe, chronic headaches and other symptoms represented an autonomic injury. He replied that he thought about it, but he decided to focus on his own areas of expertise. Tr. 149.

4. Alum

In his second report, Dr. Steinman raised a second theory about how the alum adjuvant in the HPV vaccine could cause headaches. Pet. Ex. 74 at 23. He explained, and respondent's

[34] Kinoshita, T. et al., *Peripheral Nerve Dysfunction in Adolescent Japanese Girls Following Immunization with the Human Papillomavirus Vaccination*, 53 Internal Med. 2185-2200 (2014) [Pet. Ex. 93].

experts agreed, that some vaccines, including this HPV vaccine, contain not only viral antigens but also an adjuvant which enhances the immune response to those antigens. The stronger immune response is designed to make the vaccine more effective in providing immunity to the HPV virus. In this case, the HPV vaccine at issue contains 225 micrograms of an alum adjuvant. Pet. Ex. 94.

Dr. Steinman first cited an article by Eisenbarth et al.[35] in the prestigious journal Nature. They reported that the Nalp3 inflammasome plays a crucial role in the immune-stimulatory properties of aluminum adjuvants. First, they explained: "Aluminum adjuvants are used in human vaccines to induce a potent humoral response; alum is also used as a potent adjuvant to induce T helper type 2 (TH2)-mediated inflammation in murine/ allergy models." Pet. Ex. 86 at 1124.

Eisenbarth et al. recognized that there must be two signals to activate the inflammasome—one from the antigen and one from the alum. They observed:

> [T]he alum must be encountered simultaneously with antigen *in vivo* for efficient priming[, which] suggests that the antigen might provide the first signal either directly or indirectly by inciting the production of local pro-inflammatory cytokines from resident monocytes or specialized cells recruited by alum. Once the first signal has primed the cell, alum provides the second signal for activation of the Nalp3 inflammasome.

Id. at 1125. Their study involved macrophages from mice. Some of the macrophages had normally functioning Nalp3 inflammasomes, while some were deficient. All of the samples were primed with lipopolysaccharides, then exposed to alum. The normal macrophages produced pro-inflammatory cytokines including interleukin-1 beta (IL-1β). The Nalp3-deficient macrophages did not show the same response. *Id.* at 1125. In their experiment, Eisenbarth et al. used lippopolysacchrides to provide the second signal, but they recognized that the reason that the alum was such an effective adjuvant was because the antigen in the vaccines so effectively adsorbed to the alum. *Id.* They concluded that alum adjuvants' effectiveness depends on activating the Nalp3 inflammasome, which in turn activates the production of the inflammatory cytokine IL-1β and other members of the IL-1 family including IL-18 and IL-33. They noted that the Nalp3 inflammasome is part of the innate immune response and can also direct a humoral adaptive immune response. Pet. Ex. 86, discussed at Pet. Ex. 74 at 23-24; Tr. 175.

Dr. Steinman opined that the alum adjuvant is generally beneficial in activating the innate/ inflammatory immune response, but in rare cases, it may lead to over-activation. He cited a study by Church et al.[36] for the proposition that inflammasomes are tightly regulated, with cross-talk between Nalp1 and Nalp3. Pet. Ex. 74 at 24. However, overactive inflammasomes and IL-1β are being associated with a growing number of systemic inflammatory disorders. Pet.

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[35] Eisenbarth S.C., Flavell R.A., et al., *Crucial Role for the Nalp3 Inflammasome in the Immunostimulatory Properties of Aluminum Adjuvants*, 453 Nature 1122-27, doi.10.1038/nature06939 (2008) [Pet. Ex. 86].

[36] Church L.D., G.P. Cook, and M.F. McDermott, *Primer: Inflammasomes and Interleukin 1β in Inflammatory Disorders*, Nature, doi:10.1038/ncprheum0681 (2007) [Pet. Ex. 87].

Ex. 87 at 5-6. Church et al. observed that a growing number of systemic inflammatory diseases characterized by fever, anemia and acute phase protein elevation were associated with excessive production and bioactivity of IL-1β. They suggested that the majority of these disorders appear to be caused by a missense mutation in the NACHT domain of the Nalp3 gene, which results in the dysregulated processing of IL-1β.

Dr. Steinman also cited a study by Chen et al.[37] for the proposition that activation of the Nalp3 inflammasome was associated with intracranial pain. Namely, Nalp3 is present in normal trigeminal ganglia neurons, which provides sensory innervation to the meninges and the blood vessels in the brain which are thought to be main trigger points for headache pain. Indeed, Chen et al. summarized that the Nalp3 inflammasome contributes to "the *genesis* of headaches by promoting the maturation of Il-1β in the trigeminal ganglion." Pet. Ex. 88 at 1 (emphasis added). Dr. Steinman testified that it is well documented that Il-1β is involved in the production of pain and inflammation such as in headache. Pet. Ex. 74 at 26-27; Tr. 176-77, Tr. 528. Thus, Dr. Steinman's alternative theory was that the HPV vaccine's antigens and alum, combined, can stimulate Nalp3 inflammasomes in trigeminal ganglion neurons, and the production of IL-1β resulting in headache pain.

This is essentially supported by the Martinon et al. article[38] (filed by respondent) which contained an extensive review of the role of the inflammasomes and adjuvants. Martinon et al. comprehensively reviewed the current knowledge of the inflammasome and its role in the growing knowledge of the complexity of the innate immune response in triggering the inflammatory cytokines and stimulating other signaling pathways such as the MyD88 dependent signaling pathway which is a crucial signaling molecule downstream from IL-1 and IL-18. Resp. Ex. K at 249, 252. Martinon et al. discussed the significant advances in the understanding of molecular patterns that stimulate the immune response. They noted the "fascinating" realization that:

> [A]t least one NLR [nod-like receptor] member, NALP3 . . . also detects various endogenous, sterile danger signals in the absence of microbial infections. Danger signals include several particles such as uric acid crystals, asbestos, or *aluminum*, which cause the assembly of the NALP3 inflammasome and the generation of the pro-inflammatory cytokine IL-1.

Resp. Ex. K at 254 (emphasis added). Martinon et al. also noted that "in addition to fever, IL-1β has multiple other effects on the central nervous system events [including] the induction of slow-wave sleep, anorexia, and *inflammatory pain hypersensitivity*, typically associated with infections of injury." *Id.* at 249 (emphasis added).

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[37]Chen L. et al., *Chemical Stimulation of the Intracranial Dura Activates NALP3 Inflammasome in Trigeminal Ganglia*, 1566 Brain Research 1-11 (2014) [Pet. Ex. 88].

[38] Martinon F., A. Mayor, and J. Schopp, *The Inflammasomes: Guardians of the Body*, 27 Ann. Rev. Immunol. 229-65 (2009) [Resp. Ex. K].

Respondent's expert Dr. Leist disputed this theory. He noted that Eisenbarth et al. measured a high concentration of alum at the injection site but questioned whether a significant concentration of alum would reach the brain. Resp. Ex. I at 7-8. Dr. Steinman responded that it would. The purpose of the alum and the vaccine itself is to induce a sufficiently strong response to create immunity not just at the injection site, but systemically throughout the body. That this includes the brain is evidenced by the frequent observation of fever in babies following routine vaccinations. Fever is a common indicator of immune response involving pro-inflammatory cytokines, in particular IL-1β, in the brain. Tr. 188-90. Dr. Steinman also explained how macrophages can carry foreign bodies, such as an alum adjuvant, to sites of inflammation and across the blood-brain barrier. Tr. 184-85.[39]

At the hearing, petitioner's counsel asked Dr. Steinman to address an article by Souayah et al.[40] which had been previously submitted but not explained. This was a study of VAERS reports of Guillain-Barré Syndrome ("GBS") following HPV vaccination. But significantly for this case, they observed the unusually high antigenicity of the HPV vaccine:

> Molecular mimicry and other immune system stimulation mechanisms may play a role in mediating GBS after [the HPV vaccine]. Some vaccines, such as the [HPV] vaccine, may be more likely to trigger GBS because of the high antigenicity of components of the vaccine other than the recombinant proteins (especially aluminum) and the genetic predisposition of vaccinated subjects to develop vaccine-induced autoimmunity. *The [HPV] vaccine leads to a 40 fold increase in HPV antibodies compared with the physiological antibody level triggered by a natural HPV infection. The antibody titer against the HPV genotypes 16 and 18 may remain 11 times higher than those induced by a natural infection 5.5 years after vaccination.*

Pet. Ex. 104 at 888 (emphasis added). Dr. Steinman stated that Souayah et al. demonstrated that the HPV vaccine elicits a very strong immune response. He suggested that the HPV vaccine's antigens and its alum adjuvant acting together increase the likelihood of autoimmune response. Tr. 173-74. Later in the hearing, he said that the vaccine's high antigenicity and the persistence of elevated antibodies for 5.5 years would help to explain the severity and persistence of the symptoms suffered by vaccinees such as B.A. Tr. 407.

At respondent's request, I directed Dr. Steinman and Dr. Leist to submit supplemental reports specifically addressing this article. Dr. Steinman's report was consistent with his testimony. Pet. Ex. 128. Dr. Leist contended that Souayah et al. did not help to explain the severity and persistence of a purported vaccine adverse event. He emphasized that Souayah et al. were evaluating VAERS reports of GBS following HPV vaccination. He opined that the "overwhelming majority" of cases of GBS are monophasic. Souayah et al. did not say that the subjects they studied were any different. Therefore, Dr. Leist did not believe that the long-term

[39] *Citing* Khan Z. et al., *Slow CCL2-Dependent Translocation of Biopersistent Particles from Muscle to Brain*, BioMed Central Medicine 1-18 (2013), available at http://www.biomedcentral.com/1741-7015/11/99 [Pet. Ex. 102].

[40] Souayah N. et al., *Guillain-Barré Syndrome after Gardasil Vaccination: Data from Vaccine Adverse Event Reporting System 2006-2009*, 29 Vaccine 886-89 (2010) [Pet. Ex. 104].

increase in antibody titers following HPV vaccination was associated with more severe and persistent symptoms. Resp. Ex. L at 1-2. Upon review, I do not find this argument to be persuasive. Souayah did not comment one way or another about the course of the post-vaccine adverse events they were studying. The focus of the study appeared to be on the onset of GBS in the wake of HPV vaccination rather than on the long-term outcomes of GBS. What is significant and relevant to this case is that Souayah et al. observed the significant elevation and prolonged presence of HPV antibodies. Dr. Steinman persuasively identified that finding and explained how it can relate to the prolonged, severe headaches and other symptoms experienced by B.A. and the patients studied by Brinth et al. and Kinoshita et al.

Respondent's toxicologist Dr. Cetaruk agreed that alum adjuvants probably enhance the immune response to vaccines by interacting with inflammasome pathways. Resp. Ex. G at 5. In support of that proposition, he cited Eisenbarth et al. and Martinon et al.[41] As detailed above, Martinon et al. confirms that the alum adjuvant plays an important role in stimulating the inflammasome and the ensuing response. It lends support to Dr. Steinman's theory.

Dr. Cetaruk contended that alum cannot act on its own. He stated that Eisenbarth et al. introduced lipopolysaccharide (LPS), followed by alum. Similarly, Chen et al. introduced a "soup" of inflammatory mediators, followed by alum. Dr. Cetaruk contended that in each study, first, an irritant is introduced into the brain. The trigeminal nerve senses that irritant and activates the inflammasome. He contended that alum on its own cannot serve as an irritant. It can only enhance the resulting inflammasome response. Resp. Ex. G at 5-6; Tr. 424-26, 430-38.

Dr. Cetaruk also opined that the literature submitted does not explain what happens to the trigeminal nerve after it senses an irritant and activates the inflammasome - namely, whether the trigeminal nerve continues to send out pain signals. Tr. 435-36.

Dr. Cetaruk testified that he wanted to know whether the HPV vaccine and its alum adjuvant had been associated with adverse events. He also wanted to know whether other vaccines are associated with comparable increases in antibody production. However, he agreed that Souayah et al. "introduces a possibility" that the HPV vaccine uniquely stimulates the immune system, antibody production, and adverse events. He agreed that it was probably worth further study. Tr. 502-03.

Dr. Cetaruk also stated that in his role as a medical toxicologist, he would need to see supportive medical literature on each of these points before concluding that a potential toxin (in this case, the alum adjuvant) was the cause of an injury. He described this as evidence-based medicine. He agreed this was similar to the Bradford-Hill criteria. Tr. 410-13. Dr. Steinman responded that Dr. Cetaruk was insisting on an approach that may be appropriate for clinical practice or for publication in a medical journal. However, the Vaccine Program does not require the same level of certainty. Rather, a petitioner and her expert are required to present a reputable and reliable theory of causation, based on the medical literature that is currently available. Tr. 519-30. I tend to agree. Dr. Cetaruk proposes strict scientific methodology appropriate for some clinical settings, medical literature, and public policy pronouncements. However, the Federal

[41] Martinon F., A. Mayor, and J. Schopp, *The Inflammasomes: Guardians of the Body*, 27 Ann. Rev. Immunol. 229-65 (2009) [Resp. Ex. K].

Circuit has held that the Vaccine Program does not require that level of certainty or direct proof, only a sound and reliable theory supported by a preponderance of the available evidence. *Althen*, 418 F.3d at 1280.

I accept Dr. Cetaruk's opinion to the effect that the inflammasome is activated by an irritant, then further activated by alum. But that does not contradict Dr. Steinman's opinion. Obviously, a vaccine contains antigens which are intended to cause an immune response, to which the alum adjuvant is adsorbed. In this case, the HPV vaccine contains four strains of that virus. Eisenbarth et al. observe:

> Alum must be encountered simultaneously with the antigen *in vivo* for efficient priming which suggests that the antigen might provide the first signal either directly, or indirectly by inciting the production of local pro-inflammatory cytokines from resident monocytes or specialized cells recruited by alum. Once the first signal has primed the cell, alum provides the second signal for activation of the Nalp3 inflammasome. These two signals must be sensed by the same cell for effective immune activation, thereby increasing the specificity of an immune response and perhaps explain why alum (which readily adsorbs antigens) is such an effective adjuvant.

Pet. Ex. 86 at 1125.

The vaccine antigens likely provide the initial signal, perhaps as an irritant or pathogen recognized by the Nod Like Receptor (NLR) that is then followed by the alum activation of the Nalp3 inflammasome and the enhanced production of Il-1β. When this signaling occurs in a susceptible trigeminal ganglion, it then can stimulate the pain fibers in the ganglion which provides sensory innervation to the dura and the blood vessels in the brain. Chen et al. observed, as did Dr. Steinman, that the increased production of IL-1 cytokines, namely Il-1β, can cause inflammation and pain. Pet. Ex. 88 at 2. Furthermore, the trigeminal ganglion is known to play a key role in the pathophysiology of migraines and other primary headaches. *Id* at 6. The alum contributes to the heightened effect by triggering the Nalp3 response to the initial signal from the antigens in the vaccine which likely stimulated the initial inflammatory cytokine response. Given the role of the Nalp3 inflammasome in activating the pain fibers in response to the antigen and alum in the vaccine and or the potential inflammation caused by the immune response to the vaccine, the prominence of severe headaches as a symptom may well be explained.

As he often does, Dr. Steinman recognized that the loop of knowledge in this area is not completely closed. He equated his task of offering a causation opinion in the Vaccine Program to placing stepping stones in a river. He acknowledged that his feet might get wet and he may even fall in. He contended that in this case, his stepping stones were sufficient to get him to the other side. Tr. 520. I agree. To be sure, his feet got wet. The theory was not certain and did not include the perfect experiments, which would to a large extent be difficult or impossible to conduct. The emerging role of the innate immune system in causing inflammatory reactions as well as in directing adaptive immune responses appears to be an important element of the puzzle in this case. The role of alum, which has been used as an adjuvant for many years but which has been little understood, also appears to have a likely significant role to play in triggering intracranial pain such as that suffered by B.A. Accordingly, I conclude that Dr. Steinman

presented, based on the available evidence, a sound and reliable theory to explain how, in susceptible patients, the HPV vaccine's highly effective antigens can activate and the alum adjuvant can enhance the Nalp3 inflammasome pathway in the trigeminal ganglia, which can cause severe, chronic headaches. This is likely sufficient on its own to generate the headaches, without any involvement from molecular mimicry (as Dr. Steinman first proposed).

The inflammasome theory most directly explains headaches. The connection to other symptoms is less clear. However, Dr. Steinman opined that these could be sequelae of the headaches and the resulting treatment. For example, he opined that severe, chronic headaches could contribute to depression. The anti-depressant Zoloft – which B.A. was prescribed after the onset of her headaches – can have side effects including abnormal dystonic movements. Both depression and anti-depressant medications can also be associated with decreased memory problems and decreased cognitive functioning. Pet. Ex. 59 at 3; Pet. Ex. 74 at 27-28; Pet. Ex. 89 at 2. Dr. Steinman also included light sensitivity and fatigue. Tr. 122-24. He also noted that the trigeminal ganglia are at the border of the peripheral and central nervous systems. He suggested that activation there could explain facial pain and twitching. Tr. 551.

This theory is also supported by the vaccine package insert's listing of headaches as the most common adverse event, as well as a severe event. Perhaps most compelling to suggest that a mechanism of this type may be activated by the HPV vaccine are the careful studies by Brinth and Kinoshita which reflect that many other patients experienced severe, chronic headaches along with the constellation of other symptoms presented in this case within a proximate time frame after receipt of the HPV vaccine.

5. *Althen* Prong One

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (citations omitted). The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

In *Althen*, the Federal Circuit noted that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine,* the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen,* 418 F.3d at 1280 (emphasis added). Accordingly, the first *Althen* prong may be satisfied without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu*, 569 F.3d at 1378-79 (citing *Capizzano*, 440 F.3d at 1325-26)). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not from the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking

vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, No. 2015-5097 (Fed. Cir. Jan. 3, 2017). But this does not negate or reduce a petitioner's ultimate burden to establish his overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).

Dr. Steinman offered two theories in this case. The first theory was prefaced on his diagnosis that B.A. developed ADEM. He theorized that diagnosis can be caused by molecular mimicry between peptides in the HPV vaccine and immunodominant peptides in the myelin basic protein (MBP). He devoted large parts of his reports and his testimony to molecular mimicry. He is "fascinated and deeply involved with research about molecular mimicry, and hence [he] th[ought] it adds" to his opinion. Tr. 240. As I have concluded above that there is insufficient evidence that B.A. developed ADEM, I will not discuss that theory, except to say that molecular mimicry with myelin basic protein *may* give rise to some irritation or damage that can be recognized by the pattern recognition receptors which can in turn signal to inflammasomes. However, evidence of damage to the myelin was not apparent in this case.

Dr. Steinman offered a second theory linking the high antigenicity of the HPV vaccine and its alum adjuvant to triggering the Nalp3 inflammasomes in the trigeminal ganglia giving rise to severe, chronic headaches in susceptible patients. He also stated that the second theory could work on its own. Tr. 240. As discussed above, I have concluded that this theory is sound and reliable. I will next discuss whether there is a logical sequence and effect and medically acceptable timing in B.A.'s case.

6. *Althen* Prong Two

a. Legal Standard

To fulfill *Althen* prong two, petitioner must show, by a preponderance of the evidence, "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen*, 618 F.3d at 1345.

Proof of *Althen* prong two requires a logical explanation as to how the vaccine did cause the injury in the petitioner. "A logical sequence of cause and effect' means what it sounds like—the claimant's theory of cause and effect must be logical." *Capizzano*, 440 F.3d at 1326. The proof need not rise to the level of scientific certainty, but rather to the Vaccine Act's preponderance standard under the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants.'" *Andreu*, 569 F.3d at 1378. A physician may rely on the close temporal proximity between a vaccination and an injury in concluding that there is a logical sequence of cause and effect between the vaccine and the injury. *Capizzano*, 440 F. 3d at 1326. "Requiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress . . . ." *Id.* at 1325-26.

Differential diagnosis is a reliable tool for evaluating whether there is a logical sequence of cause and effect. This has been accepted under a *Daubert* analysis by multiple courts outside the Vaccine Program. For example, the Third Circuit explained:

> We have recognized that differential diagnosis is a technique that involves assessing causation with respect to a particular individual, *In Re Paoli R.R. Yard PCB Litigation,* 35 F.3d 717, 758 (3d Cir. 1994). Differential diagnosis is defined for physicians as "the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings." Stedman's Medical Dictionary (25th ed. 1990) at 428. The elements of a differential diagnosis may consist of the performance of physical examinations, the taking of medical histories, and the review of clinical tests, including laboratory tests. A doctor does not have to employ all of these techniques in order for the doctor's diagnosis to be reliable. *See Paoli,* 35 F.3d at 759. A differential diagnosis may be reliable with less than all the types of information set out above. *See id.* Indeed as we held in *Paoli* to the extent that the district court concluded otherwise [i.e. that a differential diagnosis made on less than all types of information cannot be reliable] we hold that it abused its discretion . . . . As noted by this court in *Paoli,* evaluation of the patient's medical records is a reliable method of concluding that a patient is ill even in the absence of a physical exam.

Kannankeril v. Terminix, 128 F.3d 802, 807-08 (3d Cir. 1997); *see also Hocraffer v. Sec'y of Health & Human Servs.*, 63 Fed. Cl. 765, 777 n. 15 (2005) (noting that "[d]ifferential diagnosis or differential etiology has been accepted as reliable under the standards set forth in *Daubert* [and] by virtually every United States Court of Appeals to consider the issue.") (internal citations omitted).

b. Discussion & Analysis

As discussed above, Dr. Steinman offered a theory to explain how the HPV vaccine including its alum adjuvant *can* cause severe headaches and other symptoms. Dr. Steinman also opined that this theory fit the present case, namely, there was a logical sequence of cause and effect suggesting that the HPV vaccine *did* cause B.A. to suffer those symptoms. The first important consideration is that before the HPV vaccination on January 23, 2008, B.A. did not experience the symptoms at issue. She had experienced only relatively mild, temporary headaches that were associated with episodic colds, sinus infections, and visual strain. It is undisputed that after receiving the January 23, 2008 HPV vaccination, within approximately nine to ten days, she developed severe headaches followed by other symptoms. These were so intense that she stopped going to school and sought care from multiple specialists.

Petitioner, her counsel, and Dr. Steinman also argued that her case demonstrates challenge-rechallenge.[42] They contended that B.A.'s headaches and other symptoms, after several months of disabling intensity, settled at a lower plateau. After she received the June 3, 2008 HPV vaccination, within approximately nine to ten days, the headaches and other symptoms again became much worse. *See, e.g.*, Pet. Ex. 74 at 3. Dr. Leist disagreed, arguing that the contemporaneous records do not document a significant change of B.A.'s symptoms after the June 3 HPV vaccine. Resp. Ex. A at 7; *see also* Tr. 339-42, 345-47.

Upon review of the contemporaneous records, I note that on February 13, 2008, B.A. endorsed pain of 10 /10 to Dr. Gao. Pet. Ex. 1 at 11. On April 14, she endorsed pain of 6 / 10 to Dr. Gao. *Id.* at 10. Also on April 14, she complained of headache at 7 – 8 / 10 to her chiropractor, Dr. Wheeler. Pet. Ex. 18 at 3-4. On April 22, she complained of headaches to her gynecologist, Dr. Young. Pet. Ex. 32 at 6. She then did not have any medical appointments for approximately 42 days, which suggests a diminution in her symptoms. On June 3, she endorsed pain at 2 / 10 and then received the additional HPV vaccine at Dr. Gao's office. Pet. Ex. 1 at 9. On June 6, the psychiatrist Dr. Archibald recorded the headaches were at 6 / 10. Pet. Ex. 29 at 6-8. On June 24, Dr. Young recorded the mother's phone call that the headaches had improved but two weeks after the additional HPV vaccine, they got worse. Pet. Ex. 32 at 4. On July 10, Dr. Archibald recorded that the headaches had spiked after the additional HPV vaccine. Pet. Ex. 29 at 4. These records suggest that B.A.'s symptoms did in fact get worse after the June 3 HPV vaccine.

Her mother's November 2008 VAERS report and her affidavit are consistent with these medical records. Pet. Ex. 23 at 1; Pet. Ex. 72 at 2-3. At the hearing, she offered consistent and credible additional detail to the effect that B.A.'s symptoms had leveled out and she had been able to return to school in April, but shortly after the June 3 HPV vaccination, her symptoms escalated again. Tr. 35-38. Together, the contemporaneous records and the testimony do illustrate some level of challenge-rechallenge.

Dr. Leist also contended that if one accepts that the January 23 HPV vaccine caused an adverse immune response, one would expect the June 3 HPV vaccine to cause the same symptoms to reoccur earlier and with greater severity. Resp. Ex. A at 7. I take Dr. Leist's point, but it does not negate the records or the mother's consistent testimony. The evidence shows a second crescendo in B.A.'s symptoms within approximately the same time period after the third vaccination.

Following the theory proposed by Dr. Steinman, and after review of the extensive medical records and her mother's testimony, I conclude that petitioner has set forth a logical cause and effect relationship between the second and third doses of the HPV vaccine and her severe headache disorder and other likely secondary symptoms. These were generally consistent

[42] Challenge-rechallenge is "a paradigm for exploring whether a substance caused an adverse reaction. Under this model, an individual who has had an adverse reaction to an initial vaccine dose (the challenge event) suffers a worsening of symptoms after a second or third injection (the rechallenge event)," thereby establishing the vaccine's causal role. *Viscontini v. Sec'y of Health & Human Servs.*, No. 98-619V, 2011 WL 5842577 at *22 (Fed. Cl. Spec. Mstr. Oct. 21, 2011) (*quoting Doe/ 70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 603 (2010) (quotations omitted)), *mot. for review den'd*, 103 Fed. Cl. 600 (2012).

with the symptoms reported by the patients evaluated by Brinth and Kinoshita. While those authors considered the explanation of autonomic nervous dysfunction, Dr. Steinman presented a sound and reliable theory that the HPV vaccine's antigens and alum adjuvant activated the trigeminal ganglia in the brain, causing severe headaches. Dr. Steinman also explained how the headaches and subsequent treatment would cause the residual symptoms experienced by Brinth and Kinoshita's subjects, as well as B.A. - including headaches, dystonia, decreased memory and cognitive functioning, light sensitivity, and facial tics. Dr. Steinman offered some evidence of re-challenge following the third HPV vaccine. He also performed a reasonable and persuasive differential diagnosis for B.A. (His consideration of several alternative causes raised by the respondent is discussed below.) Accordingly, I find there is a logical sequence of cause and effect in B.A.'s case, which fits the theory accepted above.

7. *Althen* Prong Three

a. Legal Standard

Althen prong three requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 543 (2011), *recons. den'd after remand,* 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

b. Discussion & Analysis

Compared to the other causation issues discussed above, the experts did not have meaningful disagreement about the timing of this alleged vaccine injury. Dr. Steinman acknowledged that there was no case control epidemiological study on the onset of headaches following HPV vaccination. Pet. Ex. 59 at 10-11. He cited the study by Schoenberger et al.[43] which found an increased risk of GBS primarily within five weeks after swine flu vaccination. This study is frequently cited in the Vaccine Program and is a reasonable proxy for the present case, which also involves a neurological inflammatory reaction. *Id.* at 11

Dr. Steinman concluded that B.A. experienced the onset of her severe persistent headaches approximately seven to ten days after the HPV vaccination on January 23, 2008. Pet. Ex. 59 at 11; Tr. 197-98. As discussed above under *Althen* prong two, there also appears to be a

[43] Schonberger L.B. et al., *Guillain-Barré Syndrome following Vaccination in the National Influenza Immunization Program, Untied States, 1976-77*, 110 Am. J. Epidem. 105-23 (1979) [Pet. Ex. 57].

preponderance of the evidence that B.A. experienced an increase in headaches within a similar timeframe following the HPV vaccination on June 3, 2008.

Respondent's experts generally did not challenge this temporal association between petitioner's vaccinations and her symptoms. Respondent did not brief *Althen* prong three before or after the hearing. After fully considering the evidence presented, I find that petitioner has satisfied *Althen* prong three.

8. Alternative Cause

a. Legal Standard

Once petitioner establishes each of the *Althen* factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen*, 35 F.3d at 548; § 13(a)(1)(B). Respondent must demonstrate "[t]he factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition."

b. Psychiatric Component

Respondent and his expert neurologist Dr. Leist contended that petitioner may have somatoform disorder and/ or conversion disorder which contributed to her symptoms following the HPV vaccinations. Resp. Pre-Hearing Submission at 10-11.

Petitioner argued at length that I should not consider a possible psychiatric component at the outset of my analysis. *See, e.g.*, Pet. Pre-Hearing Brief at 17-19; Pet. Post-Hearing Brief at 19-26. She argued that this would be a *Broekelschen* analysis. She argued that "in order for *Broekelschen* to apply, the differential diagnosis of the dissimilar diseases must have been done by the treating doctors of petitioner, not respondent's experts, as respondent's experts can always come up with a different diagnosis." Pet. Post-Hearing Brief at 67, n. 23. Petitioner's factual foundation for this argument is not entirely correct. As discussed below, two treating neuropsychologists considered a psychological component in their evaluation of B.A. While I do not believe that the diagnosis of conversion disorder must be made by a treating physician and not an expert, that disorder is certainly a diagnosis of elimination and has significant components which should be established by either a treating doctor or a testifying expert.

Respondent did not respond to petitioner's briefing of *Broekelschen* or otherwise argue that I should consider a psychological component as an alternative cause. Respondent, relying on the treaters' records and Dr. Leist's opinion, argued that the psychiatric component "must be considered when evaluating petitioner's evidence under prong two of *Althen*." Resp. Pre-Hearing Brief at 10-11. Based on the limited evidence on the subject, I find it most appropriate to treat the psychiatric component as a possible alternative cause.

On July 31, 2008 - when B.A. had already been suffering from headaches and other symptoms for approximately six months and had missed approximately three months of school – she had an initial neuropsychological evaluation with Dr. Carter. B.A. and her mother reported that she did not have any issues before the HPV vaccinations. After the HPV vaccinations, B.A. experienced the onset of all of her symptoms – including the headaches, depression, anxiety, and cognitive disturbances. Dr. Carter seemed skeptical of a connection between the HPV vaccinations and the headaches. After administering several cognitive tests, Dr. Carter opined that there was a "significant likelihood that preexisting psychiatric disturbance (predating the onset of B.A.'s headache disorder) may explain B.A.'s extreme and unusual response to the [HPV] vaccination." However, he did not identify any particular stressor or pre-existing psychiatric disturbance. Dr. Carter's impression was generalized anxiety; severe depression; and undifferentiated somatoform disorder. Pet. Ex. 5 at 15. In June 2014, a different neuropsychologist, Dr. Griffith, wrote, based on a review of Dr. Carter's notes and the current clinical presentation: "It appears *plausible* that [B.A.]'s catastrophic reaction to the [HPV vaccine] resulted in the onset of somatoform disorder, which has evolved over time into a conversion disorder." Pet. Ex. 73 at 8 (emphasis added). While it is true that these conditions are mentioned, petitioner is correct that they were not adopted as the operative diagnosis by any of her treating medical doctors.

Respondent did not present an expert opinion explaining or interpreting the neuropsychological test results, namely the validity of Dr. Carter's conclusion that B.A. had an underlying psychological disturbance.

Respondent's expert in neurology and immunology, Dr. Leist, cited to these records to suggest that a psychiatric component could cause B.A.'s symptomatology. Resp. Ex. A at 9l Resp. Ex. I at 6; *see also* Resp. Pre-Hearing Brief at 10-11. He also discussed that when B.A. was 11 – 12 years old, she had treatment for thumb sucking, nocturia, and some recurrent episodes of abdominal discomfort. Tr. 354; *referencing, e.g.*, Pet. Ex. 1 at 75; Pet. Ex. 25 at 1. There was also some inconclusive discussion of conflict with a girl at school. Tr. 355, referencing Pet. Ex. 5 at 4-5. Dr. Leist also acknowledged that some of B.A.'s anxiety and depression could have been secondary to the severe headaches and other symptoms she suffered or even PCOS, which is discussed below. Tr. 362.

Dr. Leist was careful to only "refe[r] to what the practitioner found." Tr. 353. He just "rea[d] what the findings were." *Id.* at 354. Dr. Leist testified that if he had a patient presenting as B.A. did, he would want them to see a psychiatrist or neuropsychologist. However, he did not want to opine outside of his field of expertise. Tr. 358. Perhaps based on the limited testimony on this issue, respondent did not address it in his post-hearing brief.

Dr. Steinman responded that he did not believe that B.A. had a conversion disorder or any other psychological component which led to her physical symptoms. She had gone on an exclusive, multi-week school trip to Europe in summer 2007 and had been doing well academically. However, after the January 23, 2008 HPV vaccination, she experienced disabling headaches and other symptoms. Various medical examinations and treatments were unsuccessful. She missed school, while her friends' and classmates' lives went on. In other words, her life had come apart. Dr. Steinman opined that it was more likely that as a result of this significant disruption on her life, B.A. became depressed and anxious. Tr. 192-94.

The DSMV[44] provides that for conversion disorder (a/k/a functional neurological symptom disorder), the diagnostic criteria include:

(A) One or more symptoms of altered voluntary motor or sensory function;
(B) Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions;
(C) The symptom or deficit is not better explained by another medical or mental disorder…

DSMV at 318. The authors caution: "Although the diagnosis requires that the symptom is not explained by neurological disease, it should not be made simply because results from investigations are normal or because the symptom is 'bizarre.'" *Id.* at 319. "There must be clinical findings that show clear evidence of incompatibility with neurological disease." *Id.*

Conversion disorder appears to be a complex diagnosis that should be explained with detailed psychiatric testimony if it is to be accepted as an alternative cause. It should also have diagnostic features that contradict an alternative neurological explanation as opposed to having normal MRI findings which are present in many headache disorders as well as some cases of ADEM. Indeed, as Brinth et al. observed, their patients were initially suspected to have conversion disorder or mass hysteria. Brinth et al. concluded that explanation was unlikely given the patients' pre-vaccination history, chronic signs and symptoms, and their temporal and geographic separation from one another. Pet. Ex. 92.

I have considered the post-vaccination medical records referencing depression and anxiety. This includes the two neuropsychologists' reports suggesting an underlying psychological disturbance. However, this never became her operative diagnosis. Dr. Leist took care not to opine outside of his expertise in neurology and immunology. Respondent did not present expert psychiatric testimony favoring such a diagnosis or ruling out other possible explanations. There was no clear evidence of incompatibility with a neurological explanation for her symptoms. Thus, I find that respondent has not shown that a psychological component is a more likely than not the alternative cause for petitioner's symptoms.

c. Polycystic Ovary Syndrome ("PCOS")

Respondent, through Dr. Leist, contended that PCOS may also have contributed to petitioner's symptomatology. Resp. Pre-Hearing Brief at 10-11. Prior to the hearing, Dr. Leist noted that B.A. had weight gain "between 2007 and 2008", menstrual irregularity, abnormal hair growth, elevated serum testosterone, and elevated insulin levels. She was diagnosed with PCOS. Resp. A. at 6-7; *see also* Pet. Ex. 21 at 1-2 (March 2011 assessment including "mild PCOS" by gynecologist/ reproductive endocrinologist Dr. Stradtman).

[44] American Psychiatric Association, The Diagnostic and Statistical Manual of Mental Disorders (5th ed. 2013) (hereinafter "DSMV").

Dr. Leist submitted an article by Rackow[45] which was a comprehensive review of PCOS. However, he did not discuss in his reports or indicate what he found to be most significant to this case. Rackow cautions about the difficulty of diagnosing PCOS, particularly in adolescent women because the presentation of normal puberty and PCOS can have overlapping features such as menstrual irregularity, acne, and mild irregular hair growth. Resp. Ex. E at 282. According to Rackow, there are no formal diagnostic criteria for PCOS in adolescents. *Id.* There are several diagnostic frameworks for PCOS in adults. The Rotterdam criteria, which is apparently gaining support, includes a positive finding of polycystic ovaries on ultrasound. *Id.* at It does not appear that B.A. underwent this test. This comprehensive article on PCOS does not mention headaches, which are her overriding complaint.

Dr. Leist also submitted a study by Cosar et al.[46] on 30 young women with diagnosed PCOS (based on the Rotterdam criteria, referenced above) who also had severe headaches. He submitted this article because of the finding that the majority of these subjects had normal MRIs. He opined: "In the context of [PCOS]… you can have a headache condition that is greater than 8 out of 10 that can be diagnosed with a normal brain MRI." Tr. 372-74. However, Cosar et al. do not address the commonality of the co-occurrence of PCOS and headaches. Additionally, their focus was on the relationship between PCOS, headaches, and idiopathic intracranial hypertension ("IIH"), as indicated by the title of the study. This article is of limited relevance because as noted above, B.A. seemingly did not undergo an ultrasound to confirm the diagnosis of mild PCOS. Additionally, B.A. did not have IIH. She underwent two lumbar punctures to obtain cerebrospinal fluid, in March 2008 and in April 2009. Opening pressure on both tests was normal, making IIH unlikely. Pet. Ex. 59 at 3; Pet. Ex. 74 at 1. Neither was IIH diagnosed by her treating physicians. *Id.*[47]

Dr. Leist stated that if he suspects that a patient has PCOS, he refers them to a gynecologist and he is not an expert in that condition. Tr. 316. As with the psychiatric component, respondent did not address PCOS in post-hearing briefing or present expert testimony to support this diagnosis as an alternative cause. At most, PCOS can be said to be another diagnostic confounder in this case without any expert support for its role in B.A.'s symptoms. I do not find it to be a more likely alternative cause.

d. Unspecified Infection

Dr. Leist also opined that an infection was a "likely proximate event to the worsening of her headache symptoms," based on the contemporaneous medical records. Resp. Ex. A at 7. Namely, at the first appointment following the vaccination, on January 30, 2008, Dr. Gao recorded petitioner was experiencing new headaches alongside sore neck, sore throat, nausea,

[45] Rackow B.W., *Polycystic Ovary Syndrome in Adolescents*, 24 Curr. Opin. Gynecol. 281-87 (2012) [Resp. Ex. E].

[46] Cosar E. et al., *Polycystic Ovary Syndrome is Related to Idiopathic Intracranial Hypertension According to Magnetic Resonance Imaging and Magnetic Resonance Venography*, 89 Fertil. Steril. 1245-46 (2008) [Resp. Ex. C].

[47] This is a key distinction from another special master's recent decision involving HPV vaccinations, headaches, and Dr. Steinman testifying on behalf of the petitioner. *Rolshoven v. Sec'y of Health & Human Servs.,* No. 14-439V, 2018 WL 1124737, *21 (Fed. Cl. Spec. Mstr. Jan. 11, 2018) (noting that once the petitioner was correctly diagnosed with and treated for IIH, "her headaches mostly resolved").

cough, and congestion. Pet. Ex. 1 at 13. At the next visit on February 5, 2008, B.A. reported similar symptoms plus fever. However, Dr. Gao recorded that her temperature was at 97.1 degrees Fahrenheit, which would not constitute a fever. Pet. Ex. 1 at 12. Dr. Leist opined that based on these symptoms, it was reasonable to suspect that B.A. had an infection. However, the chest x-ray did not find evidence of pneumonia. The sinus CT scan probably ruled out significant accumulation of fluid in the sinuses. However, these tests did not definitively exclude an infection. According to Dr. Leist, one possibility would be an upper respiratory infection (URI), which would not necessarily present with fever. Dr. Leist could not identify any treating physician's record diagnosing B.A. with an infection. Tr. 335-38. Additionally, the January 30, 2008 record indicates that she tested negative for streptococcus infection, which eliminated from consideration one of the common infections in the upper respiratory tract. Pet. Ex. 1 at 13.

Dr. Steinman had several responses to this argument. *See* Pet. Post-Hearing Brief at 66-75. Of note, he opined that he would weigh a "known" factor such as the HPV vaccination over an "unknown" factor such as an unconfirmed infection. Pet. Ex. 72 at 2-3.

As noted above, the burden of proof is shifted to respondent to establish a more likely or principal cause of the injury alleged. Respondent must show a specified and documented alternative cause. § 13(a); *Knudsen*, 35 F.3d at 548; *Deribeaux*, 717 F.3d at 1369. In the present case, even if B.A. had some symptoms consistent with an infection, several types of infection were ruled out. Additionally, respondent and his expert Dr. Leist did not locate any treating physician's opinion that an infection caused her severe, persistent headaches and various other symptoms. Upon consideration, I find that respondent has not presented preponderant evidence for this possible alternative cause.

VI. Conclusion

This case presented a particularly difficult causation question. While many of our cases in this court are close calls, this one was particularly so. But based on a review of the entire record and for the foregoing reasons, I have concluded that petitioner has satisfied the more likely than not criteria for causation. She is entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/ Thomas L. Gowen
Thomas L. Gowen
Special Master